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Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: An Update of a 2008 Comparative Effectiveness Review

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Statement of Funding and Purpose

This report is based on research conducted by the ECRI Institute Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2007-10063). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (generally known by its acronym, CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to: epc@ahrq.hhs.gov.

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Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: An Update of a 2008 Comparative Effectiveness Review

Structured Abstract

Objective. To comprehensively review and update the effectiveness and harms of treatments for clinically localized prostate cancer.

Data Sources. MEDLINE®, PreMEDLINE, and EMBASE®, the Cochrane Library, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, gray literature, and the U.K. National Health Service Economic Evaluation Database from January 01, 2007, through January 23, 2013.

Review Methods. We synthesized evidence from randomized controlled trials (RCTs) and nonrandomized comparative studies published in English that evaluated treatments and reported clinical or biochemical outcomes in patients with clinically localized prostate cancer.

Results. Seven RCTs and 20 nonrandomized comparative studies evaluating numerous treatment options met inclusion criteria. However, no given comparison was represented by more than one or two studies, so for most comparisons (particularly those performed in nonrandomized studies) the strength of evidence (SOE) was insufficient. The exceptions are summarized below.

The Scandinavian Prostate Cancer Group-4 (SPCG-4) trial reported data on all-cause and prostate cancer–specific mortalities at the end of the 15-year followup period that favored RP over watchful waiting (strength-of-evidence [SOE]: low). Data at 12-year followup from SPCG-4 and The Prostate Intervention Versus Observation Trial (PIVOT) was inconclusive for these outcomes. Findings from subgroup analyses suggesting the advantage of RP might be associated with younger age and higher PSA levels were somewhat inconsistent between trials (SOE: insufficient).

Two RCTs that each compared EBRT versus EBRT plus ADT both reported an improvement in overall survival and prostate cancer-specific mortality among men who received EBRT plus ADT (SOE: low). Findings from subgroup analyses suggesting that the advantage of EBRT plus ADT might be associated with lower comorbidity and intermediate risk levels were not confirmed in both trials (SOE: insufficient).

The definition and severity of adverse events varied greatly across studies. Adverse events such as urinary incontinence, bowel incontinence, and erectile dysfunction were mostly reported among men who underwent RP. Conversely, adverse events such as genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction were reported among men who received radiation therapy.

Conclusions. The evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits. Although limited evidence favors RP over watchful waiting and EBRT plus ADT over EDT, the patients most likely to benefit and the applicability of these study findings to contemporary patients and practice remain questionable. More RCTs that can control for many of the unknown and known confounding factors that can affect long-term

outcomes are needed to evaluate comparative risks and benefits of a number of therapies for clinically localized prostate cancer.

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Executive Summary

Prostate cancer is the most common nondermatologic cancer in men.[1,2] The American Cancer Society estimates that in 2012, 241,740 men were expected to receive a diagnosis of prostate cancer and 28,170 were expected to die from the disease.[1] Approximately 90 percent of those who receive such a diagnosis have cancer confined to the prostate gland (clinically localized disease). Since 2004, the prostate cancer incidence rate has decreased by 2.7 percent annually among men 65 years of age or older and has remained steady among men younger than age 65.[1] The major risk factors for prostate cancer are advanced age, race, and ethnicity (the highest incidence is in blacks), and family history.

Many cases of prostate cancer have a protracted course if left untreated. Many men die with prostate cancer, rather than from it.[3] During its early stages, clinically localized prostate cancer is usually asymptomatic.[4] However, as the cancer grows, it may cause urinary problems, such as blood in the urine, pain or a burning sensation during urination, a weak urine stream, inability to urinate, and frequent urination, especially at night. These presenting symptoms, along with a physical examination, prostate-specific antigen (PSA) levels, and biopsy, may be used to evaluate patients for the presence of prostate cancer.

The practice of evaluating healthy men with no prostate symptoms for prostate cancer is controversial. The PSA test is used to measure blood levels of PSA, a protein produced by the prostate gland.[4] Elevated PSA levels may indicate the presence of prostate cancer, but elevations are also seen in conditions such as benign prostatic hyperplasia and prostatitis. In contrast, some patients with prostate cancer do not have elevated levels of PSA.[5] In recent years, more frequent use of PSA testing has intensified concern about overdiagnosis of prostate cancer (i.e., detection of cancer that would have remained silent and caused the patient no illness throughout his lifetime).[2,4]

In May 2012, the U.S. Preventive Services Task Force recommended against PSA-based screening for prostate cancer in healthy men of all ages, concluding that the harms of screening outweigh the benefits (Grade D recommendation).[6] This recommendation, however, remains controversial among health care professionals. Potential benefits of regular PSA screening include early cancer detection and reduced mortality rates. Potential harms include anxiety related to abnormal results, pain, infection, bleeding due to diagnostic biopsies, and the morbidity of definitive treatment in men who may not need such treatment.[7-10]

Determining which men with clinically localized prostate cancer are most likely to benefit from interventions such as surgery and radiation could potentially improve the balance of benefits and harms, especially in those identified by screening. Current practice is to use tumor grade as the primary prognostic variable in patients with clinically localized prostate cancer.[2] After biopsy confirms the presence of the cancer, pathologists report tumor grade using the Gleason score, which ranges from 2–10.[4] Gleason 8–10 tumors are considered the most aggressive, Gleason 7 tumors are considered somewhat less aggressive, and Gleason 6 or lower tumors are considered potentially indolent.[11] Although the primary measure of tumor aggressiveness is the Gleason histologic score, efforts are under way to identify more reliable prognostic factors. PSA/PSA kinetics and digital rectal examination are still very important when deciding treatment. Additionally, radiographic imaging in high-risk disease is valuable, along with other diagnostic assessments before making definitive treatment decisions.

Staging is the process of assessing whether the cancer is confined to the prostate gland or has spread and to what extent.[4] Staging of prostate cancer could be clinical (based on a digital rectal examination of the prostate gland, prostate biopsy, and laboratory tests) or pathological (based

on surgery and examination of resected prostate tissue). The staging system currently used is the American Joint Committee on Cancer TNM classification.[4] The TNM classification is based on the extent of primary tumor (T stages), whether cancer has spread to the adjacent lymph nodes (N stages), and any metastasis (M stages).[4,12] The TNM categories are combined with the Gleason histologic score and PSA results (stage grouping) to determine the overall stage, which is commonly reported as Stages I, IIA, IIB, III, and IV, with stage I being the least advanced and stage IV being the most advanced. In the absence of a Gleason histologic score, staging can still be based on the TNM classification.

Another categorization incorporating PSA levels, Gleason histologic score, and TNM stage stratifies tumors into low-, intermediate-, and high-risk (in terms of their likelihood of progressing with no treatment or recurring after early intervention).[4]

- Low risk (corresponding to stage I): a PSA level of 10 ng/mL or less, a Gleason score of 6 or less, and a clinical stage of T1c or T2a
- Intermediate risk (roughly corresponding to stage IIA): a PSA level of 10–20 ng/mL, a Gleason score of 7, or a clinical stage of T2b but not qualifying for high risk
- High risk (roughly corresponding to stage IIB): a PSA level of more than 20 ng/mL, a Gleason score of 8–10, or a clinical stage of T2c

Clinicians make pretreatment assessment of whether prostate cancer is localized by determining tumor stage, basing their decision on a clinical examination (principally by digital rectal examination). Prostate cancer that is believed to be confined to the prostate gland (T1–T2, NX, M0; or stage I–II) is considered clinically localized[4] and is the focus of this report.

Therapies for Clinically Localized Prostate Cancer

The primary goal of treating clinically localized prostate cancer is to target the men most likely to need intervention to prevent disability or death while minimizing intervention-related complications. Frequently used treatment options include the following:

- Radical prostatectomy (RP), including laparoscopic or robotic-assisted prostatectomy
- External beam radiotherapy (EBRT), including conventional radiation, intensity-modulated radiation (IMRT), three-dimensional conformal radiotherapy (3-D-CRT), stereotactic body radiation therapy, and proton beam therapy
- Interstitial brachytherapy (BT)
- Cryotherapy
- Hormonal therapy
- Observation or watchful waiting (WW) (the two terms are used interchangeably throughout the report)
- Active surveillance
- High-intensity focused ultrasound (HIFU)

Choice of treatment options may be influenced by factors such as patient age and health at the time of the diagnosis, life expectancy, estimated likelihood of cancer progression without treatment, the surgeon's experience and preference, and treatment-related convenience, costs, and potential for eradication and adverse effects (e.g., incontinence, sexual dysfunction).[4] Before choosing any intervention, an assessment of the overall health status of patients is important because it may influence response to therapy, severity of complications, and life expectancy.[4]

The National Cancer Institute and the Centers for Disease Control and Prevention sponsored a National Institutes of Health (NIH) State-of-the Science Conference in December 2011 to

better understand the risks and benefits of active surveillance and other observational management strategies for PSA screening–detected, low-grade, localized prostate cancer.[3] The panel concluded that active surveillance should be offered to patients with low-risk prostate cancer. Active surveillance usually includes hands-on followup in which PSA levels are checked, prostate biopsies may be repeated, and subsequent treatment is planned.[3]

The NIH panel used the term "watchful waiting" to describe a palliative observational strategy—that is, waiting for symptoms to appear and then intervening to manage the symptoms. In the 2008 comparative effectiveness review (CER) that we are updating, "Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer," these two approaches were considered together.[13] In the literature, the distinction between active surveillance (with curative intent) and other observational strategies (with palliative intent) has not always been clear; however, for this systematic review update we attempted to separate the two using the definitions proposed at the NIH State-of-the-Science Conference in 2011.[3]

Scope and Key Questions

This report updates a 2008 CER conducted by the University of Minnesota EPC. A surveillance analysis conducted by the Southern California EPC in May 2012 determined the need for this update. In the analysis, investigators evaluated the key questions (KQs) from the 2008 CER and conducted a restricted literature search for new evidence.[14] The key finding of the analysis was that the Prostate Cancer Intervention Versus Observation Trial (PIVOT),[14-16] published after the 2008 report, has outdated conclusions. Specifically, the analysis suggested that KQs 1, 2, and 4 should be reevaluated because newly available evidence from the PIVOT trial and other recent studies may change the conclusions from those of the previous report.[14]

This update examined the same four KQs as the original 2008 report on the comparative effectiveness of treatments for clinically localized prostate cancer. Although these KQs were reviewed and approved by the Agency for Healthcare Research and Quality (AHRQ) and discussed with Technical Expert Panel (TEP) members for the original report, we presented them for discussion with a newly convened TEP for this update and made changes as necessary. This update summarized the more recent evidence comparing the relative effectiveness and safety of treatment options for clinically localized prostate cancer. We addressed the following KQs:

Key Question 1

What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?

a. RP, including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches
b. EBRT, including standard therapy and therapies designed to decrease exposure to normal tissues such as 3-D-CRT, IMRT, proton beam therapy, and stereotactic body radiation therapy
c. Interstitial BT
d. Cryotherapy
e. WW
f. Active surveillance
g. Hormonal therapy
h. HIFU

Key Question 2

How do specific patient characteristics (e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences such as trade-off of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these therapies overall and differentially?

Key Question 3

How do provider/hospital characteristics affect outcomes of these therapies overall and differentially (e.g., geographic region, case volume, learning curve)?

Key Question 4

How do tumor characteristics (e.g., Gleason score, tumor volume, screen-detected vs. clinically detected tumors, and PSA levels) affect the outcomes of these therapies overall and differentially?

PICOTS Criteria

The key questions identified the following PICOTS (population, interventions, comparators, outcomes, timing, and setting) parameters.

Population

- KQs 1–4: Men considered to have clinically localized prostate cancer (T1–T2, N0–X, M0–X) regardless of age, histologic grade, or PSA level. Articles were excluded if men with disease stage higher than T2 were enrolled, and outcomes were not stratified by stage.

Interventions

- For KQs 1–4, we included treatment options for men with clinically localized prostate cancer: RP (including retropubic, perineal, laparoscopic, robotic-assisted), WW, active surveillance, EBRT (including conventional radiation, IMRT, 3D-CRT, proton beam, and stereotactic body radiation therapy), BT, hormonal therapy, HIFU, and cryotherapy.

Comparators

- Any interventions of interest listed above.

Outcomes

- The primary outcome is overall mortality or survival. Additional outcomes include prostate cancer–specific mortality or survival, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, and quality of life (QOL). We focused primarily on common and severe adverse events of treatment, including bowel, bladder, and sexual dysfunction, as well as harms from biopsy such as bleeding and nosocomial infections.
- For KQ 3, we searched outcomes after radical prostatectomy, the most common treatment for localized prostate cancer, in association with provider location, case volume, and affiliation with academic centers.

Timing

- Duration of followup was appropriate for the outcome under consideration.

Settings

- No restrictions by setting.

We also prepared an analytic framework illustrating the relationship between the KQs and the outcomes of interest (see Figure 1 in main body of report).

Methods

Search Strategy

Literature searches were performed for the time period January 1, 2007, through January 23, 2013, by medical librarians who followed established systematic search protocols. For all KQs, we searched the following databases on the OVID SP platform using the one-search and deduplication features: MEDLINE, PreMEDLINE, and EMBASE. We also searched the Cochrane Library (including the Central Register of Controlled Trials, the Cochrane Database of Methodology Reviews, and the Cochrane Database of Systematic Reviews), the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, gray literature, and the U.K. National Health Service Economic Evaluation Database for unique reviews, trials, economic analyses, and technology assessments. We also used resources available through the EPC Scientific Resource Center to access Scientific Information Packets.

Study Selection

We used the same study selection criteria as in the 2008 report. For KQs 1, 2, and 4, we included randomized trials only if the randomized treatment allocation was based on men with clinically localized disease and if clinical outcomes were reported for T1 and T2 disease separately from T3 and T4 disease. In the absence of any randomized trials, large nonrandomized comparative studies ($n \geq 500$) that employed a matching procedure to ensure baseline comparability of treatment groups were considered for inclusion. For KQ 3, we included multicenter or comparative observational studies that examined the effect of provider characteristics on the diagnosis and treatment of localized prostate cancer.

Data Extraction and Management

We used the DistillerSR® (Evidence Partners Inc., Ottawa, Ontario, Canada) Web-based systematic review software for abstract screening and data extraction. Each team member's data extraction was reviewed by one other team member. Also, because of the possibility of subjective interpretation, the risk-of-bias items were judged in duplicate. We resolved all discrepancies through discussion. Two researchers extracted study, patient, tumor, and intervention characteristics and predefined outcomes onto standardized forms. Standard errors, regression coefficients, and 95 percent confidence interval (95% CI) were calculated from reported means, standard deviations, and sample size when provided/appropriate.[17] Multiple publications of the same study (e.g., publications reporting subgroups, other outcomes, longer followup) were identified by examining author affiliations, study designs, enrollment criteria, and enrollment dates.

Risk-of-Bias Assessment of Individual Studies

Because of the possibility of subjective interpretation, assessment of methodologic risk of bias of individual studies was performed by two researchers for each study, and discrepancies were resolved by consensus. When consensus could not be reached, a third researcher adjudicated. We assessed the risk of bias by following the guidelines in the chapter, "Assessing the risk of bias of individual studies when comparing medical interventions" in the "Methods Guide."[18]

For KQs 1, 2, and 4, we assessed the risk of bias for the studies by evaluating several items such as randomization, allocation concealment, intention-to-treat-analysis, and completeness of followup. Additionally, we assessed fidelity to the protocol to address performance bias and blinding of outcome assessors to address detection bias when outcomes are subjective. To be considered as having low risk of bias, the study must have met all the following conditions: randomization of study participants to treatment groups; concealment of allocation; data analysis based on the intention-to-treat-principle; if outcome assessors were not blinded or blinding of outcome assessors was not reported, then the outcome must have been objective; a difference of 15 percent or less in the length of followup for the comparison groups; more than 85 percent of enrolled patients provided data at the time point of interest; and good fidelity to the protocol.

To be considered as having high risk of bias, the study must have met at least one of the following criteria: trial did not randomly assign patients to study groups and did not blind outcome assessors; trial had a difference of 15 percent or less in the length of followup for comparison groups; or trial did not have good fidelity to the protocol. To be considered as having medium risk of bias, the study met neither the criteria for low risk of bias nor the criteria for high risk of bias.

Data Synthesis

Because of the differences in study designs, treatments, patient and tumor characteristics, and reporting of outcomes, the 2008 report did not pool studies for KQs 1, 2, and 4. For the same reason, we performed only qualitative analysis in this update. Since RCTs and nonrandomized comparative studies differed substantially in average risk of bias, we performed separate qualitative analyses and present results separately for these study designs. We further stratified results based on comparisons across primary treatment categories and comparisons within primary treatment categories. Generally, we reported summaries of effectiveness and adverse-event outcomes with ranges according to treatment option, tumor characteristics, and group sample size. For KQ 1, we summarized and discussed comparative risks, benefits, and outcomes of therapies. For KQ 2, we summarized how patient characteristics affect outcomes. For KQ 4, we summarized how tumor characteristics affect outcomes.

Strength of the Body of Evidence

We provided evidence ratings for the following patient-oriented outcomes: overall mortality or survival, prostate cancer–specific survival, and quality of life. We assessed strength of evidence by following the guidelines from the publication, "Grading the Strength of a Body of Evidence When Comparing Medical Interventions," by Owens et al.[19] We graded the SOE based on the following domains: risk of bias (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), and precision (precise or imprecise). Two independent graders assessed each domain, and differences were resolved by consensus.

The SOE was allotted an overall grade of high, moderate, low, or insufficient as outlined by Owens et al.[19] The decision to grade an evidence base as insufficient rather than low usually reflected an imprecise effect estimate (a nonstatistically significant effect with 95% confidence intervals wide enough to allow the possibility of a significant benefit for one treatment compared with another) in an evidence base with only one or two studies. Evidence from a single study with medium or high risk of bias was also graded as insufficient. When evidence came from subgroup analyses (KQ2 and KQ4), the strength of evidence was lowered by one level. For example, when the strength of evidence for a primary analysis in KQ1 was low, strength of evidence for subgroup analyses from the same studies was considered insufficient. This is because subgroup analyses were often not prespecified in the study protocol, were often underpowered to detect differences between treatments, and generally should be considered as hypothesis-generating rather than definitive analyses.

Assessing the Applicability of the Evidence for Each Key Question

Applicability assessment refers to how generalizable findings from this report are to other populations and settings. Applicability was assessed by following the guidelines in the publication, "Assessing the Applicability of Studies When Comparing Medical Interventions," by Atkins et al.[20] The applicability of the evidence involves the following five aspects: patients, interventions, comparisons, outcomes, and settings.[20] We addressed factors relevant to the applicability of the evidence by evaluating patient selection in both observational studies and clinical trials. We considered the primary biology and epidemiology (grade and stage of the prostate cancer) and the present-day clinical practice setting. The typical interventions, comparisons, outcomes (e.g., overall mortality, prostate cancer–specific survival), and settings of care were also used to more clearly specify the most applicable study characteristics (i.e., most typical of localized prostate cancer care in the United States).

Results

The results are organized according to study design and specific comparisons addressed under each key question.

Results of Literature Searches

Our searches of the literature identified 3,081 potentially relevant articles. We excluded 816 articles by reviewing the titles, 2,126 by reviewing the abstracts, and 107 by reviewing the full-length articles. Figure 2 in the main report is a flow chart that describes in detail the exclusion process and the reasons for the exclusion at each review level. The remaining 32 publications describing 27 unique studies made up the evidence base for this review. Thirty-two articles describing 27 unique studies addressed KQ 1, 6 studies addressed KQ 2, and 8 studies addressed KQ 4.

Key Question 1. What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?

a. RP, including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches

b. EBRT, including standard therapy and therapies designed to decrease exposure to normal tissues such as 3-D-CRT therapy, IMRT, proton beam therapy, and stereotactic body radiation therapy
c. Interstitial BT
d. Cryotherapy
e. WW
f. Active surveillance
g. Hormonal therapy
h. HIFU

Randomized Controlled Trials

Seven RCTs in 12 unique publications addressed this KQ. Three studies[16,21,22] were categorized as medium risk of bias for all their reported outcomes. Two studies[23,24] were categorized as low risk of bias for all their reported outcomes. One study[25] was categorized as low risk of bias for all outcomes except for QOL, which was rated medium risk of bias. One study[26] was categorized as medium risk of bias for all outcomes except for QOL, which was rated high risk of bias. Common reasons for assigning a medium risk of bias to the studies were lack of concealment of allocation and lack of outcome assessor blinding. Assignment of high risk of bias occurred when a subjective outcome such as QOL was assessed in a study with lack of concealment of allocation and lack of outcome assessor blinding.

The most commonly compared procedures were RP versus observation or WW (2 studies)[16,25] and EBRT versus EBRT plus androgen deprivation therapy (ADT) (2 studies).[24,26] The remaining three studies compared radical retropubic prostatectomy versus BT,[21] ADT versus ADT plus EBRT,[23] and retropubic versus perineal prostatectomy.[22]

Nonrandomized Comparative Studies

Twenty nonrandomized comparative studies (n≥500) addressed this KQ. All 20 studies were categorized as high risk of bias for all of their reported outcomes. None of the trials blinded outcome assessors. Reporting of subjective outcomes was also common. The most commonly compared procedures robotic radical prostatectomy versus radical retropubic prostatectomy (3 studies).[27-29]

The remaining studies compared the following:

- RP versus 3D-CRT versus BT[30]
- RP versus EBRT (3D-CRT or IMRT) versus BT[31]
- RP versus observation[32]
- BT versus EBRT plus BT versus ADT[33]
- Open RP versus robotic RP versus cryotherapy versus BT[34]
- Robotic prostatectomy versus open retropubic prostatectomy[35]
- Conservative management versus ADT[36]
- Observation versus radiotherapy[35]
- BT versus cryotherapy[37]
- Conservative management versus RP[38]
- BT versus image guided-EBRT versus high-dose-rate EBRT[39]
- IMRT versus 3D-CRT[40]
- BT versus BT plus ADT[41]

- BT versus EBRT versus EBRT plus BT[42]
- RP versus EBRT versus observation[43]
- RP versus EBRT[44]
- IMRT versus proton beam therapy versus 3D-CRT[45]

Key Question 2. How do specific patient characteristics (e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences such as tradeoff of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these therapies overall and differentially?

We identified four RCTs[16,24-26] and two nonrandomized comparative studies[32,41] that addressed this KQ.

Key Question 3. How do provider/hospital characteristics affect outcomes of these therapies overall and differentially (e.g., geographic region, case volume, learning curve)?

We did not identify any comparative study that addressed this KQ.

Key Question 4. How do tumor characteristics (e.g., Gleason score, tumor volume, screen-detected vs. clinically detected tumors, PSA levels) affect the outcomes of these therapies overall and differentially?

We identified three RCTs[16,25,26] and five nonrandomized comparative studies[31-33,36,41] that addressed this KQ.

Key Findings and Strength of Evidence

Twenty-seven studies (32 publications) met the inclusion criteria for review for KQ 1. Six of the 27 studies also met the inclusion criteria for KQ 2, and 8 of them further met the inclusion criteria for KQ 4. Studies that addressed KQ1 reported overall data for patient-oriented outcome measures such as overall survival, all-cause mortality, prostate cancer–specific mortality, QOL, and adverse events. Evidence addressing KQ 2 or KQ 4 came solely from subgroup analyses of some larger studies that addressed KQ 1. Although these subgroup analyses reported data on overall survival, all-cause mortality, or prostate cancer–specific mortality for specific patient subgroups, they did not report adverse events that occurred in these subgroups.

Table A summarizes our findings on the major health outcomes from RCTs for KQ 1. These outcomes include overall survival, all-cause mortality, prostate cancer–specific mortality, and QOL (reported using a global QOL score), for which we have assessed the SOE.

For the comparison of RP versus WW, the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial reported data on all-cause and prostate cancer–specific mortality at the end of the 15-year followup period, and the finding favors RP with a low SOE grade. At the end of the 12-year followup period, the PIVOT reported a nonsignificant trend toward lower prostate cancer–specific mortality with RP compared with observation. Neither trial compared RP to active surveillance. Both the PIVOT and SPCG-4 studies reported data on all-cause and prostate cancer–specific mortalities at the end of the 12-year followup period, but we found the evidence on these outcomes at this time point was insufficient to draw any conclusion.

We did not perform a meta-analysis on this outcome primarily because of the difference in enrolled patient populations between the two trials. In comparison to the SPCG-4 trial, the PIVOT study enrolled a higher percentage of men with nonpalpable tumors (T1c, 50%t vs. 12%) and with low PSA values.[46] The SPCG-4 trial used an eligibility criterion of T1 or T2 stage, but without widespread PSA screening in the early portion of the study, these tumors are at higher risk of being understaged by digital rectal examination than PSA screened tumor in PIVOT. The two trials also differed in their protocol for the observation arms. In the SPCG-4 trial, transurethral resection of the prostate (TURP) was recommended as the initial treatment for men with urinary obstruction, and hormonal treatment was recommended for men with disseminated disease (before January 2003) or as the patient's physician advised it (after January 2003). In the PIVOT study, patients with symptomatic local progression are treated first with alpha blockers or mechanical intervention (e.g., TURP). Hormonal therapy is considered first-line therapy for patients with disease progression requiring nonmechanical therapy. Patients with disease that continues to progress or fails to respond to hormonal therapy underwent radiotherapy or chemotherapy. In the PIVOT study, patients with symptomatic local disease progression despite mechanical therapy and alpha blockers could also undergo prostatectomy. The evidence on other patient-oriented outcomes based on the two trials is also insufficient to permit conclusions. These findings should always be interpreted with caution.

For the comparison of radical retropubic prostatectomy versus BT, the evidence on the only reported outcome, QOL at 1 year, was insufficient to allow any conclusion.

For the comparison of EBRT alone versus EBRT combined with ADT, the data on overall survival and prostate cancer–specific mortality reported in the trials favors the combined treatments with a low SOE grade. The evidence on other patient-oriented outcomes is insufficient to permit conclusions. The findings from these trials should be interpreted with a thorough consideration of the specific patient populations that were heterogeneous and the treatment methods used in these trials. For example, treating low-risk patients with EBRT plus ADT would be considered substantial overtreatment by most national clinical guidelines. The D'Amico et al. study[24] did not include these patients, and the Jones et al. study[26] found no difference in this subgroup. Additionally, the radiation dose in both of these trials was low, and the length of ADT (only 4 months) in the Jones et al. study[26] might be too short for patients with high-risk disease.

Table B summarizes our findings on the patient-oriented outcomes from the nonrandomized comparative studies. Due to high risk of bias and the small number of studies for each comparison/outcome combination, the SOE was insufficient for all nonrandomized treatment comparisons.

The definition and severity of adverse events varied greatly across the studies. Adverse events such as urinary incontinence, bowel incontinence, and erectile dysfunction were mostly reported among men who underwent RP. Conversely, adverse events such as genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction were reported among men who received radiation therapy.

Table A. Summary of the main findings from randomized controlled trials for Key Question 1

Evidence Base	Comparison	Patient-oriented Outcomes	Findings	SOE Grade
SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality at 15 years	Favors RP RR 0.75; 95% CI, 0.61 to 0.92	Low

Table A. Summary of the main findings from randomized controlled trials for Key Question 1 (continued)

Evidence Base	Comparison	Patient-oriented Outcomes	Findings	SOE Grade
SPCG-4 trial, 2011[25]	RP vs. WW	Prostate cancer–specific mortality at 15 years	Favors RP RR 0.62; 95% CI, 0.44 to 0.87	Low
SPCG-4 trial, 2008[46] and PIVOT study, 2012[16]	RP vs. WW	All-cause mortality at 12 years	Inconclusive PIVOT: no significant difference between interventions SPCG-4 trial: no significant difference between interventions	Insufficient
SPCG-4 trial, 2008[46] and PIVOT, 2012[16]	RP vs. WW	Prostate cancer–specific mortality at 12 years	Inconclusive SPCG-4 trial: favors RP RR 0.65, 95% CI, 0.45 to 0.94 PIVOT: no significant difference between interventions	Insufficient
SPCG-4 trial, 2011[47]	RP vs. WW	Quality of life (median followup of 12.2 years)	Inconclusive	Insufficient
Giberti et al., 2009[21]	Radical retropubic prostatectomy vs. brachytherapy	Quality of life at 1 or 5 years	Inconclusive	Insufficient
Jones et al., 2011[26] and D'Amico et al. 2008[24]	EBRT vs. EBRT plus ADT	Overall survival	Favors EBRT plus ADT The findings from the included studies were statistically significant in the same direction.	Low
D'Amico et al., 2008[24]	EBRT vs. EBRT plus ADT	All-cause mortality (median followup of 7.6 years)	Inconclusive	Insufficient
Jones et al., 2011[26] and D'Amico et al., 2008[24]	EBRT vs. EBRT plus ADT	Prostate cancer–specific mortality	Favors EBRT plus ADT The findings from the included studies were statistically significant in the same direction.	Low
Widmark et al., 2009[23]	ADT vs. EBRT plus ADT	Prostate cancer–specific mortality at 10 years	Inconclusive	Insufficient

For the interpretation of SOE grading, refer to AHRQ's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews"[48]

ADT=Androgen-deprivation therapy; EBRT=external beam radiotherapy; PIVOT=Prostate Intervention Versus Observation Trial; RP=radical prostatectomy; RR=relative risk; SPCG-4=Scandinavian Prostate Cancer Group-4; WW=watchful waiting.

Table B. Summary of the main findings from nonrandomized comparative studies for Key Question 1

Evidence Base	Comparison	Patient-oriented Outcomes	Findings	SOE Grade
Abdollah et al., 2012[32]	Radiotherapy vs. observation	PCSM at 10-year followup	Inconclusive evidence No significant difference between treatments	Insufficient

Table B. Summary of the main findings from nonrandomized comparative studies for Key Question 1 (continued)

Evidence Base	Comparison	Patient-oriented Outcomes	Findings	SOE Grade
Kibel et al., 2012[31]	RP vs. EBRT (3D-CRT plus IMRT) vs. BT	Overall survival and PCSM at 10 year followup	Inconclusive evidence Overall survival higher with RP than EBRT or BT PCSM lower with RP than EBRT No significant difference in PCSM between RP and BT	Insufficient
Rosenberg et al., 2012[33]	BT plus EBRT vs. BT plus ADT	PCSM at 4.4- and 4.8-year followup for the 2 treatment cohorts, respectively	Inconclusive evidence PCSM lower with BT plus ADT	Insufficient
Shen et al., 2012[42]	BT vs. EBRT vs. BT plus EBRT	PCSM after a median followup of 6.4 years	Inconclusive evidence PCSM lower with BT or BT plus EBRT over EBRT	Insufficient
Abdollah et al., 2011[49]	RP vs. observation	PCSM and other-cause mortality at 10-year followup	Inconclusive evidence PCSM lower with RP	Insufficient
Hadley et al., 2010[38]	RP vs. conservative management	All-cause mortality and PCSM	Inconclusive evidence Multivariable analysis: Favor RP Propensity score adjustment: Favor RP Instrumental variable analysis: no significant different between compared treatments	Insufficient
Dosoretz et al., 2010[41]	BT vs. BT plus ADT	All-cause mortality after a median followup of 4.8 years	Inconclusive evidence Mortality lower with BT plus ADT	Insufficient
Lu-Yao et al., 2008[36]	Primary ADT vs. conservative management	Overall and prostate cancer–specific survival and mortality after a median followup of 81 months	Inconclusive evidence Conservative management had better overall mortality and prostate cancer–specific mortality or survival No significant difference in overall survival between the 2 treatments.	Insufficient
Krambeck et al., 2008[28]	Radical retropubic prostatectomy vs. robotic-assisted radical prostatectomy	QOL, PCSM, and other-cause mortality after a median followup of 1.3 years	Inconclusive evidence No significant difference between the treatment groups	Insufficient
Albertsen et al. 2007[43]	Surgery vs. radiation vs. observation	Prostate cancer–specific survival and overall survival at 13-year followup	Inconclusive evidence Both survival outcomes higher with RP than radiation or observation	Insufficient
Ferrer et al. 2007[30]	RP vs. 3D-CRT vs.BT	QOL at 2-year followup	Inconclusive evidence No significant difference in Short Form-36 between treatment groups	Insufficient

3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; BT=brachytherapy; EBRT=external beam radiotherapy; IMRT=intensity-modulated radiation therapy; PCSM=prostate cancer–specific mortality; QOL=quality of life; RP=radical prostatectomy.

For KQ 2, two RCTs that compared RP and WW and another two RCTs that compared EBRT alone and EBRT plus ADT performed subgroup analysis according to patient characteristics. The reported findings from subgroup analysis are summarized in Table C. In the PIVOT trial[16], investigators reported no differences in all-cause mortality and prostate cancer–specific mortality when stratified according to age between RP and WW. In contrast, investigators in the SPCG-4 trial[25] reported that the advantages of RP over WW in all-cause mortality and prostate cancer–specific mortality were statistically significant for patients younger than 65 years of age but not the older patient group.

In the study by D'Amico et al.[24], the authors reported that EBRT plus ADT was associated with significantly lower 8-year all-cause mortality in comparison with EBRT alone for patients with no comorbidity or a minimal comorbidity score. However, for patients with a moderate or severe comorbidity score, all-cause mortality did not differ significantly between the two treatments. None of the included studies reported adverse events based on patient characteristics. For reasons described in the Methods section, all subgroup analyses were considered inconclusive with insufficient SOE.

Table D summarizes our findings on the patient-oriented outcomes from the nonrandomized comparative studies that addressed KQ 2.

Table C. Summary of the findings from randomized controlled trials for Key Question 2

Evidence Base	Comparison	Outcome	Patient Characteristics by Which Data Were Stratified	Findings	SOE Grading
PIVOT, 2012[16] and SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality and PCSM	Age	Inconclusive evidence PIVOT: no significant association with age SPCG-4: Age <65 years significantly associated with benefit of RP	Insufficient for patient subgroup
PIVOT, 2012[16]	RP vs. WW	All-cause mortality and PCSM	Race, self-reported performance status	Inconclusive evidence No significant associations	Insufficient for patient subgroup
D'Amico et al., 2008[24]	EBRT vs. EBRT plus ADT	8-year all-cause mortalityl	Comorbidity scores	Inconclusive evidence Minimal or no comorbidity significantly associated with increased mortality with EBRT alone	Insufficient for patient subgroup
Jones et al., 2011[26]	EBRT vs. EBRT plus ADT	10-year overall survival and PCSM	Age, race	Inconclusive evidence No significant associations	Insufficient for patient subgroup

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; RP=radical prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4; WW=watchful waiting.

Table D. Summary of the findings from nonrandomized comparative studies for Key Question 2

Evidence Base	Comparison	Outcome	Patient Characteristics by Which Data Were Stratified	Findings	SOE Grading
Dosoretz et al., 2010[41]	Brachytherapy (BT) vs. BT plus androgen deprivation therapy (ADT)	All-cause mortality at a median followup of 4.8 years	Age	Inconclusive evidence Significant association with increased all-cause mortality with increasing age (>73 years) in BT plus ADT group	Insufficient for patient subgroup
Abdollah et al., 2012[32]	Observation vs. ADT	Prostate cancer–specific mortality at 10-year followup	Age, Charlson comorbidity score	Inconclusive evidence Age 75-80 years significantly associated with benefit of ADT Comorbidity scores did not alter benefit of ADT	Insufficient for patient subgroup

For KQ 3, we did not identify any comparative study that directly examined how provider characteristics influence the effectiveness of different treatments. As a result, this current review does not add new information to that reported in the 2008 report on the same KQ.

For KQ 4, two RCTs that compared RP and WW and another RCT that compared EBRT alone and EBRT plus ADT performed subgroup analysis according to tumor characteristics. The reported findings from the subgroup analyses are summarized in Table E. In the PIVOT trial[16], investigators reported that RP did not reduce all-cause mortality and prostate cancer–specific mortality among men with PSA <10 ng/mL but resulted in a significant reduction among men with PSA >10 ng/mL. In contrast, investigators in the SPCG-4 trial[25] reported that the PSA level (<10 vs. >10 ng/mL) did not alter RP's effect in reducing all-cause mortality or prostate cancer–specific mortality. In the trial by Jones et al.,[26] the addition of short-term ADT to EBRT led to a significantly higher overall survival and lower prostate cancer–specific mortality among patients with intermediate-risk prostate cancer, but not among patients with high- or low-risk prostate cancer. None of the included studies reported adverse events based on tumor characteristics. For reasons described in the Methods section, all subgroup analyses were considered inconclusive with insufficient SOE.

Table F summarizes our findings on the patient-oriented outcomes from the nonrandomized comparative studies that addressed KQ 4.

Table E. Summary of the main findings from randomized controlled trials for Key Question 4

Evidence Base	Comparison	Outcome	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grading
PIVOT, 2012[16] and SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality and PCSM	PSA	Inconclusive evidence PIVOT: significant association with PSA (>10 ng/mL) and RP benefit SPCG-4: PSA level did not alter benefit of RP	Insufficient for patient subgroup
SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality and PCSM	Gleason score	Inconclusive evidence No significant association	Insufficient for patient subgroup
PIVOT, 2012[16]	RP vs. WW	All-cause mortality and PCSM	Risk level based on PSA, Gleason score, or tumor stage	Inconclusive evidence No significant association	Insufficient for patient subgroup

Table E. Summary of the main findings from randomized controlled trials for Key Question 4 (continued)

Evidence Base	Comparison	Outcome	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grading
SPCG-4 trial, 2011l[25]	RP vs. WW	All-cause mortality and PCSM	Risk level based on PSA, Gleason score, or a WHO grade of 1	Inconclusive evidence Low-risk group showed same benefit of RP observed in overall cohort; findings for high-risk group not reported	Insufficient for patient subgroup
Jones et al., 2011[26]	EBRT vs. EBRT plus ADT	10-year overall survival and PCSM	Risk level based on PSA, Gleason score, or tumor stage	Inconclusive evidence Intermediate risk level significantly associated with benefit of EBRT plus ADT	Insufficient for patient subgroup

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; PSA=prostate-specific antigen; RP=radical prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4; WHO=World Health Organization; WW=watchful waiting.

Table F. Summary of the main findings from nonrandomized comparative studies for Key Question 4

Evidence Base	Comparison	Outcome	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grading
Dosoretz et al., 2010[41]	BT vs. BT plus ADT	All-cause mortality at a median followup of 4.8 years	PSA, Gleason score, and clinical T classification	Inconclusive evidence No significant associations	Insufficient for patient subgroup
Rosenberg et al., 2012[33]	BT plus EBRT vs. BT plus ADT	PCSM at median followup of 4.4 years and 4.8 years, respectively	PSA, Gleason score	Inconclusive evidence Both variables significantly associated with higher PCSM in BT plus EBRT group	Insufficient for patient subgroup
Kibel et al., 2012[31]	RP vs. EBRT vs. BT	Overall survival and PCSM at 10-year followup	Tumor risk (high, intermediate, low)	Inconclusive evidence No significant associations	Insufficient for patient subgroup
Abdollah et al. 2012[32]	Observation vs. EBRT	PCSM at 10-year followup	Tumor risk (high, intermediate, low)	Inconclusive evidence High risk significantly associated with benefit of EBRT	Insufficient for patient subgroup
Lu-Yao et al., 2008[36]	Conservative management vs. ADT	All-cause mortality and PCSM at 81-month followup	Tumor risk (poorly differentiated, moderately-differentiated)	Inconclusive evidence Moderately-differentiated tumors were significantly associated with higher mortality in ADT group	Insufficient for patient subgroup

ADT=Androgen-deprivation therapy; Brachytherapy=BT; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; PSA=prostate-specific antigen; RP=radical prostatectomy

Applicability and Implications for Clinical Decisionmaking

Although the restrictions on the applicability of the conclusions may vary across the evidence bases for different treatment comparisons, some restrictions may be common to most of these evidence bases. All the RCTs included in this review recruited the patients before 2002. Since then, the treatment options compared in many studies have greatly evolved. For example, open surgery was the main treatment technique for RP in the reviewed RCTs. However, in recent

years, robotic-assisted surgery has become the dominant technique for RP in the United States. Similarly for EBRT, BT, and other treatments, advances in technologies and knowledge have helped many of these treatments better target the cancer, improving the effectiveness of and the tolerance to the treatments. As a result, the evidence based on dated medical techniques may not apply to the current practice. Therefore, future high-quality studies are required to validate the comparative effectiveness and safety of the current and emerging treatment techniques (e.g., robotic-assisted surgery, proton beam, stereotactic body radiation therapy).

Additionally, the patients studied in the RCTs included in this review may have a different risk profile from the patients whose diagnosis of prostate cancer is established at the current time. Ten to 15 years ago, prostate cancers were primarily detected based on digital rectal examination or tissue specimens obtained during transurethral resection of the prostate for treatment of benign prostatic obstruction. Currently, the vast majority of prostate cancers detected in the United States are found due to PSA testing. Men often start to receive PSA tests in their 40s and continue taking the test on a regular basis until their 80s. As a result, the patients whose diagnosis is established can be younger and have a more confined cancer than those studied in the reviewed RCTs, which further restricts the applicability of the reviewed evidence. Because of intensified concern about overdiagnosis of prostate cancer in recent years, the way to use PSA testing for screening prostate cancer and the criteria for establishing an abnormal PSA test result may continue to change. Patient and tumor characteristics among men with prostate cancer diagnosed in the future are likely to be different.

Despite the restricted applicability of the evidence, the current review may still inform some important treatment decisions that patients with localized prostate cancer face. Overall, the body of evidence for the treatment of prostate cancer continues to evolve. Extended followup data from SPCG-4 and the recently published PIVOT trial add to our understanding of the effects of RP versus WW or observation in subgroups. Neither study compared RP to active surveillance. The SOE from the SPCG-4 is rated as low for all-cause mortality and prostate cancer–specific mortality at 15 years (meaning that there is low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate of effect). The SOE from the SPCG-4 and PIVOT trials is rated as insufficient for all-cause mortality and prostate cancer–specific mortality at 12 years (meaning that the evidence does not permit a conclusion). Our review was unable to draw any conclusions about the effect of various treatments on global QOL. Therefore, it is unclear how patients as a whole will balance the trade-off between the potential benefit in long-term survival and the potential harms (e.g., urinary and bowel incontinence, sexual dysfunction) associated with the surgery. Ultimately, the treatment decision rests with each individual patient, his family, and his physicians. These stakeholders' personal preferences and values play a significant role in this decisionmaking process. This may be particularly true for patients with life expectancies fewer than about 15 years.

This review and the 2008 report both attempted to evaluate whether a particular patient group (in terms of age, race, general health status, and various tumor risk factors) might benefit more from a compared intervention. Addressing this question would help patients and clinicians make better-informed treatment decisions. However, the evidence reviewed does not provide any consistent conclusion on this issue. For example, the SPCG-4 trial found that RP led to significantly lower all-cause and cancer-specific mortalities compared with WW among patients younger than 65 years of age but not among the older patient group.[16] However, the PIVOT study did not have the same finding regarding age.[25] The PIVOT trial found that RP did not reduce all-cause or cancer-specific mortality among men with PSA of less than 10 ng/mL but

resulted in a significant reduction among men with PSA of more than 10 ng/mL. However, this finding is only partially confirmed by the SPCG-4 trial, which found that overall mortality was reduced by RP regardless of PSA level. Although their findings differ for patients with PSA less than 10 ng/mL, the two trials show some overlap in findings (reduced mortality with RP) for the subgroup of patients with PSA greater than 10 ng/mL. Nevertheless, enough inconsistency remains in the evidence that clear guidance regarding the appropriate patient population for RP is difficult to establish.

This current review also reached some conclusions for the comparison of EBRT alone versus EBRT combined with ADT. The evidence based on two RCTs[24,26] suggests that the results for overall survival and prostate cancer–specific mortality favored the combined treatments with a low SOE grade. The evidence also suggests that the advantage of EBRT combined with ADT may only occur among patients with no comorbidity or a minimal comorbidity score, who are white and younger than 70 years of age. However, this evidence is weak and requires further validation by future studies before it can be used to form clinical guidance for choosing appropriate cases for the treatments. Similarly, the evidence for other treatment comparisons covered in the current review also need further validation, particularly via rigorously designed RCTs, to form a more reliable foundation for making clinical recommendations.

Limitations and Research Gaps

This current review has several limitations. First, although more RCTs were available for this review than for the 2008 report, the amount of evidence from well-designed RCTs that directly compare different treatments, particularly emerging technologies (e.g., proton beam therapy, HIFU), is still small. The few RCTs that met the inclusion criteria for the review compared only a few treatments (e.g., RP vs. WW, EBRT alone vs. EBRT plus ADT) of interest. Questions about the effectiveness and safety of new and emerging treatment methods are largely unanswered by RCTs.

Second, all the reviewed RCTs were conducted more than 10 years ago. The manner in which PSA testing was used for detecting prostate cancer and the treatment techniques used may not reflect current practice, so their results may not be generalizable to current practice settings. Third, there was little reporting of outcomes according to major patient and tumor characteristics. The reviewed RCTs that performed subgroup analyses according to patient or tumor characteristics often did not have adequate power to detect significant effects within the subgroups.

Finally, wide variation existed in reporting and definitions of outcomes and tumor and patient characteristics, which makes evidence synthesis difficult. Additionally, this review includes only studies published in English. The review also used specific sample size cutoffs as a criterion to exclude small-sized studies. Inclusion of small-sized studies and those published in other languages may have resulted in additional conclusions or may have contradicted some conclusions. Furthermore, this review limited evidence to studies that reported T1 and T2 disease separately from T3 or T4 disease. Studies that did not report data separately (e.g., reporting data for T1, T2, T3, and T4 disease together) were excluded. As a result, some information potentially relevant to the topic of this review may be missed.

To further address the KQs of this review, additional RCTs are needed. In Table 68 and Table 69 in Appendix H, we provide a summary of six ongoing clinical trials: four in the United States; one in Canada; and one in the United Kingdom (ProtecT [Prostate testing for cancer and Treatment]). Ideally, future RCTs should recruit patients with PSA-detected prostate

cancer and compare patient-focused outcomes (e.g., all-cause and cancer-specific mortalities, QOL) between treatment options and techniques used in the current practice with a long followup. These RCTs should use standardized or validated methods to determine patient outcomes and have adequate power to detect significant treatment effect.

High-quality observational studies (e.g., cancer registries and large prospective cohort studies that appropriately adjust for baseline differences between the groups) may also provide useful evidence, particularly in cases in which large differences in outcomes might exist. Observational studies may help estimate treatment effectiveness in high-priority patient and tumor subgroups that have not been adequately addressed in RCTs. Findings from observational studies may also help generate hypotheses and design better RCTs. We noted that some observational studies conflicted in their findings based on the analytic methods employed (e.g., propensity score vs. instrumental variable approaches). Studies inconsistently defined and reported outcomes. Most of the existing evidence comes from nonrandomized comparative studies with treatment selection biases.

Finally, we did not identify any studies that compared active surveillance to current treatment therapies. Since WW or observation is not active surveillance, more studies are needed to assess the effectiveness of active surveillance. A major gap that we identified was the fact that, although outcomes of surgery and radiation are influenced by center/surgeon volume and or expertise, most of these studies did not provide any information of practice of care that could have influenced the results in any of the included studies. More randomized trials that can control for many of the unknown and known confounding factors that can affect long-term outcomes are needed to evaluate comparative risks and benefits of a number of therapies for clinically localized prostate cancer.

Conclusions

Overall, the body of evidence for the treatment of prostate cancer continues to evolve, but the evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits. Extended followup data from SPCG-4 and the recently published PIVOT trial add to our understanding of the effects of RP versus WW or observation in subgroups, but further clarification is needed. Neither study compared RP to active surveillance. The SOE on overall and prostate cancer–specific mortality from the SPCG-4 trial at 15-years followup are rated as low (i.e., low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate of effect) and favored RP in men with clinically detected localized prostate cancer. At 12-years followup, the evidence from the PIVOT and SPCG-4 trials on both outcomes is rated as insufficient. For the comparison of EBRT alone versus EBRT combined with ADT, the data on overall survival and prostate cancer–specific mortality reported in two trials favors the combined treatments with a low SOE grade. However, the patients most likely to benefit and the applicability of these findings to contemporary populations and practice remain questionable. Therefore, the findings from the surgical and radiotherapy trials should be interpreted with a thorough consideration of the specific patient populations and the treatment methods used in the trials. More RCTs that reflect contemporary practice and can control for many of the unknown and known confounding factors that can affect long-term outcomes are needed to evaluate comparative risks and benefits of a number of therapies for clinically localized prostate cancer.

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Introduction

Prostate cancer is the most common nondermatologic cancer in men.[1,2] American Cancer Society data show that in 2012, an estimated 241,740 men were expected to receive a diagnosis of prostate cancer and 28,170 were expected to die from the disease.[1] Approximately 90 percent of those who receive such a diagnosis have cancer confined to the prostate gland (clinically localized disease). Since 2004, the prostate cancer incidence rate has decreased by 2.7 percent annually among men 65 years of age or older and has remained steady among men younger than age 65.[1] The major risk factors for prostate cancer are advanced age, race, and ethnicity (the highest incidence is in blacks), and family history.

Many cases of prostate cancer have a protracted course if left untreated. Many men die with prostate cancer, rather than from it.[3] During its early stages, clinically localized prostate cancer is usually asymptomatic.[4] However, as the cancer grows, it may cause urinary problems, such as blood in the urine, pain or a burning sensation during urination, a weak urine stream, inability to urinate, and frequent urination, especially at night. These presenting symptoms along with a physical examination, prostate-specific antigen (PSA) levels, and biopsy may be used to evaluate patients for the presence of prostate cancer.

The practice of evaluating healthy men with no prostate symptoms for prostate cancer is controversial. The PSA test is used to measure blood levels of PSA, a protein produced by the prostate gland.[4] Elevated PSA levels may indicate prostate cancer, but elevations are also seen in conditions such as benign prostatic hyperplasia and prostatitis. In contrast, some patients with prostate cancer do not have elevated levels of PSA.[5] In recent years, more frequent use of PSA testing has intensified concern about overdiagnosis of prostate cancer, that is, detection of cancer that would have remained silent and caused the patient no illness throughout his lifetime.[2,4]

In May 2012, the U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer in healthy men of all ages, concluding that the harms of screening outweigh the benefits (Grade D recommendation).[6] This recommendation, however, remains controversial among health care professionals. Potential benefits of regular PSA screening include early cancer detection and reduced mortality rates. Potential harms include anxiety related to abnormal results, pain, infection, bleeding due to diagnostic biopsies, and the morbidity of definitive treatment in men who may not need such treatment.[7-10]

Landmark trials, including the European Randomized Study of Screening for Prostate Cancer (ERSPC), the Göteborg trial (from the Swedish center in the ERSPC trial), and the U.S.-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial have published findings on the effect of PSA screening on prostate cancer mortality. Both the ERSPC and PLCO trials found little effect on mortality following PSA screening.[50] The Göteborg trial reported a 0.40 percent absolute risk reduction in prostate cancer mortality, a relative risk reduction of 44 percent, and no difference in overall mortality in men aged 50–64 years over 14 years of screening.[51]

Citing these trials, the USPSTF assessed the potential benefit of screening to be zero to one death from prostate cancer prevented for every 1,000 men aged 55–69 years screened by PSA testing every 1 to 4 years for 10 years. They also estimated that there would be 100–120 men with false-positive tests and 110 men with true-positive tests; among the latter, rates of complications from treatment would range from fewer than 1 death per 1,000 men to 29 cases of erectile dysfunction per 1,000 men screened and treated.[6] For these reasons, determining which men with clinically localized prostate cancer are most likely to benefit from interventions such as surgery and radiation could potentially improve the balance of benefits and harms, especially in

those identified by screening. Current practice is to use tumor grade as the primary prognostic variable in patients with clinically localized prostate cancer.[2] After biopsy confirms the presence of the cancer, pathologists report tumor grade in terms of the Gleason score, which ranges from 2 to 10.[4] Gleason 8–10 tumors are considered the most aggressive, Gleason 7 tumors are considered somewhat less aggressive, and Gleason 6 or lower tumors are considered potentially indolent.[11] Although the primary measure of tumor aggressiveness is the Gleason histologic score, efforts are under way to identify more reliable prognostic factors. PSA/PSA kinetics and digital rectal examination are still very important when deciding treatment. Additionally radiographic imaging in high-risk disease is valuable before making definitive treatment decisions.

Staging is the process of assessing whether the cancer is confined within the prostate gland or has spread beyond and, if so, to what extent it has spread.[4] Staging of prostate cancer could be clinical (based on a digital rectal examination of the prostate gland, prostate biopsy, and laboratory tests) or pathological (based on surgery and examination of resected prostate tissue). The staging system currently used is the American Joint Committee on Cancer TNM classification.[4] The TNM classification is based on the extent of primary tumor (T stages), whether cancer has spread to the adjacent lymph nodes (N stages), and any metastasis (M stages).[4,12] These classifications are detailed in Table 1, Table 2, and Table 3.

Table 1. Tumor (T) stages

Stage	Description
T1	The tumor cannot be felt or seen using imaging techniques
	T1a. The cancer cells are incidentally found in 5% or less of resected tissue
	T1b. The cancer cells are found in more than 5% of the resected tissue
	T1c. The cancer is identified by needle biopsy, which is performed because of high prostate-specific antigen levels
T2	The cancer is confined to the prostate but can be felt as a small, well-defined nodule
	T2a. The cancer is in half of a prostate lobe
	T2b. The cancer is in more than half of a prostate lobe
	T2c. The cancer is in both prostate lobes
T3	The tumor extends through the prostate capsule
	T3a: The cancer extends outside the prostate but not to the seminal vesicles
	T3b: The cancer has spread to the seminal vesicles
T4	The tumor is fixed or invades adjacent structures

Table 2. Lymph node (N) stages

Stage	Description
NX	Nearby lymph nodes were not assessed
N0	The cancer has not spread to any nearby lymph nodes
N1	The cancer has spread to one or more nearby lymph nodes in the pelvis

Table 3. Metastasis (M) stages

Stage	Description
M0	The cancer has not spread past nearby lymph nodes
M1	The cancer has spread beyond nearby lymph nodes
	M1a. The cancer has spread to distant (outside the pelvis) lymph nodes
	M1b. The cancer has spread to bone
	M1c. The cancer has spread to other organs such as the lungs, liver, or brain (with or without spread to the bones)

Because of the limited sensitivity of pretreatment evaluations, some men who have received a diagnosis of clinically localized prostate cancer may actually have cancer that has spread outside the prostate gland. Unfortunately, additional assessments such as radiographs, bone scans, computed tomography (CT), and magnetic resonance imaging (MRI) are of limited use, particularly for detecting small foci of cancer in lymph nodes. Several methods for improving detection via imaging are under study. For detecting cancer in the lymph nodes, an innovative technique called enhanced MRI may help.[12] For identifying prostate cancer in other parts of the body, a new type of positron-emission tomography scan that uses the radioactive tracer carbon acetate as a replacement for fluorodeoxyglucose may be useful; it may also be used to define the effectiveness of the therapy.[12]

The TNM categories are combined with the Gleason histologic score and PSA results (stage grouping) to determine the overall stage, which is commonly reported in Roman figures (Stages I, IIA, IIB, III, and IV), with stage I being the least advanced and stage IV being the most advanced. In the absence of a Gleason histologic score, staging can still be based on the TNM classification. The criteria for Stages I and II are provided in Table 4 below:

Table 4. Anatomic and prognostic staging

Stage Group	T*	N	M	PSA (ng/mL)	Gleason
I	T1a–c	N0	M0	PSA<10	Gleason ≤6
	T2a	N0	M0	PSA<10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA<20	Gleason 7
	T1a–c	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA<20	Gleason 7
	T2b	N0	M0	PSA<20	Gleason ≤7
IIB	T2b	N0	M0	PSA X	Gleason X
	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8

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*Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

X=Unknown.

Another categorization incorporating PSA levels, Gleason histologic score, and TNM stage stratifies tumors into low-, intermediate-, and high-risk (in terms of their likelihood of progressing with no treatment or recurring after early intervention).[4]

- Low risk (corresponding to stage I): a PSA level of 10 ng/mL or less, a Gleason score of 6 or less, and a clinical stage of T1c or T2a
- Intermediate risk (roughly corresponding to stage IIA): a PSA level of 10–20 ng/mL, a Gleason score of 7, or a clinical stage of T2b but not qualifying for high risk
- High risk (roughly corresponding to stage IIB): a PSA level of more than 20 ng/mL, a Gleason score of 8–10, or a clinical stage of T2c

Clinicians make pretreatment assessment of whether prostate cancer is localized by determining tumor stage, basing their decision on a clinical examination (principally by digital

rectal examination). Prostate cancer that is believed to be confined to the prostate gland (T1–T2, NX, M0; or stage I–II) is considered clinically localized[4] and is the focus of this report.

Therapies for Clinically Localized Prostate Cancer

The primary goal of treating clinically localized prostate cancer is to target the men most likely to need intervention to prevent disability or death while minimizing intervention-related complications. Treatment options that are frequently used include the following, which are described in Table 5:

- Radical prostatectomy (RP), including laparoscopic or robotic-assisted prostatectomy
- External beam radiotherapy (EBRT), including conventional radiation, intensity-modulated radiation therapy (IMRT), three-dimensional conformal radiation (3D-CRT), stereotactic body radiation therapy, and proton beam radiation
- Interstitial brachytherapy (BT)
- Cryotherapy
- Hormonal therapy
- Observation or watchful waiting (WW) (these terms will be used interchangeably)
- Active surveillance
- High-intensity focused ultrasound (HIFU)

Table 5. Treatment options for clinically localized prostate cancer

Treatment Option	Treatment Description
Radical prostatectomy (open retropubic, open perineal, laparoscopic, robotic-assisted approaches)	Complete surgical removal of prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes
EBRT, including conventional radiation, intensity-modulated radiation therapy, 3D conformal radiation, proton beam, and stereotactic body radiation therapy	Multiple doses of radiation from an external source applied over several days to weeks
Interstitial brachytherapy	Radioactive implants placed using radiologic guidance. Low-dose-rate/permanent implants and high-dose-rate brachytherapy may be used. Combination therapy comprises EBRT with a brachytherapy boost
Cryotherapy	Destruction of cells through rapid freezing and thawing, using transrectal guided placement of probes and injection of freezing/thawing gases
Hormonal therapy	Oral or injection medications or surgical removal of testicles to lower or block circulating androgens
Observation or watchful waiting (WW) (these terms will be used interchangeably)	Relatively passive patient followup, with symptom management if and when any symptoms occur[3]
Active surveillance	Usually includes hands-on followup in which prostate-specific antigen levels are checked, prostate biopsies may be repeated, and subsequent treatment is planned[3]
High-intensity focused ultrasound therapy	Tissue ablation of the prostate by intense heat, focusing on the identified cancerous area

3D=Three-dimensional; EBRT=external beam radiation therapy.

Choice of treatment options may be influenced by factors such as patient age and health at the time of the diagnosis, life expectancy, estimated likelihood of cancer progression without

treatment, the surgeon's experience and preference, and treatment-related convenience, costs, and potential for eradication and adverse effects (e.g., incontinence, sexual dysfunction).[4] Before choosing any intervention, an assessment of the overall health status of patients is important because it may influence response to therapy, severity of complications, and life expectancy.[4]

The treatment for men with clinically localized prostate cancer has been the subject of much debate. As discussed above, identifying those men most likely to benefit from aggressive therapy is challenging. Ideally, those with slowly progressing disease who are more likely to die of other causes would be spared unnecessary treatment, while those men with aggressive localized prostate cancer would be offered curative procedures.[3,10] One option currently under study for assessing disease progression is an approach called "active surveillance," which typically includes monitoring of PSA levels and rate of increase, periodic digital rectal examination, and repeat prostate biopsies.

The National Cancer Institute and the Centers for Disease Control and Prevention sponsored a National Institutes of Health (NIH) State-of-the Science Conference in December 2011 to better understand the risks and benefits of active surveillance and other observational management strategies for PSA screening–detected, low-grade, localized prostate cancer.[3] The panel members concluded that active surveillance should be offered to patients with low-risk prostate cancer.

The NIH panel used the term "watchful waiting" to describe a palliative observational strategy—that is, waiting for symptoms to appear and then intervening to manage the symptoms. In the 2008 comparative effectiveness review (CER) that we are updating, "Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer," these two approaches were considered together.[13] In the literature, the distinction between active surveillance (with curative intent) and other observational strategies (with palliative intent) has not always been clear; however, for this systematic review update we attempted to separate the two using the definitions proposed at the NIH State-of-the-Science Conference in 2011.[3]

Findings From the Original Report

The 2008 CER on therapies for clinically localized prostate cancer, written by the University of Minnesota Evidence-based Practice Center (EPC), included 18 randomized controlled trials (RCTs) and 473 observational studies.[13] None of the included studies enrolled patients with prostate cancer primarily identified by PSA testing. The main findings of the 2008 report include the following:

- No single therapy can be considered the preferred treatment for localized prostate cancer because of limitations in the body of evidence as well as the likely trade-offs a patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary across treatments.
- No RCT reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity.
- The results from the analysis of national administrative databases and surveys suggested that provider/hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. Patient outcomes varied in different locations and were associated with provider and hospital case volume, independent of patient and disease characteristics. Screening practices and treatment choices varied by

physician specialty and across regions of the United States. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.

- Few data exist on the comparative effectiveness of treatments based on stratification of risk into low, intermediate, and high categories using PSA levels, histologic score, and tumor volume.

Overall, the authors concluded that "assessment of the comparative effectiveness and harms of localized prostate cancer treatments is difficult because of limitations in the evidence."[13] For example, only a few RCTs directly compared the effectiveness between (rather than within) major treatment categories. Additionally, many of these RCTs were inadequately powered to provide long-term survival outcomes, with the majority reporting biochemical progression or recurrence as the primary outcomes. Finally, some RCTs were conducted before prostate cancer detection with PSA testing was available.

Some of the remaining issues and future research needs that were outlined in the 2008 report included the following[13]:

- RCTs should evaluate relative effectiveness and adverse events and stratify their findings based on patient (e.g., age, race, comorbidity) and tumor (e.g., level of PSA, stage, histologic grade) characteristics.
- Comparative trials on technologies that were considered to be "emerging" at the time the report was written—intensity-modulated radiation therapy, proton beam radiation, cryotherapy, and robotic-assisted and laparoscopic prostatectomy—must provide long-term followup data.
- Head-to-head RCTs must be adequately powered to compare primary treatments for localized prostate cancer.
- Trials should standardize reporting of key clinically relevant outcomes and should structure the assessment of outcome measures such as quality of life and health status.

Rationale for Update

A surveillance analysis conducted by the Southern California EPC in May 2012 determined the need for this update. In the analysis, investigators evaluated the Key Questions (KQs) from the 2008 CER and conducted a restricted literature search for new evidence.[14] The key finding of the analysis was that the Prostate Cancer Intervention Versus Observation Trial (PIVOT),[14-16] published after the 2008 report, makes its conclusions out of date. Specifically, the analysis suggested that KQs 1, 2, and 4 should be reevaluated, as newly available evidence from the PIVOT trial and other recent studies may change the conclusions from those of the previous report.[14]

I. Scope and Key Questions

This update examined the same four KQs as in the original 2008 report on the comparative effectiveness of treatments for clinically localized prostate cancer. Although these KQs were reviewed and approved by the Agency for Healthcare Research and Quality (AHRQ) and discussed with Technical Expert Panel (TEP) members for the original report, we presented them for discussion with a newly convened TEP for this update and made changes as necessary. This update summarized the more recent evidence comparing the relative effectiveness and safety of treatment options for clinically localized prostate cancer. The KQs we addressed are as follows:

Key Question 1

What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?

a. RP, including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches
b. EBRT, including standard therapy and therapies designed to decrease exposure to normal tissues such as IMRT, 3D-CRT, proton beam therapy, and stereotactic body radiation therapy
c. Interstitial BT
d. Cryotherapy
e. WW
f. Active surveillance
g. Hormonal therapy
h. HIFU

Key Question 2

How do specific patient characteristics (e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences such as trade-off of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these therapies overall and differentially?

Key Question 3

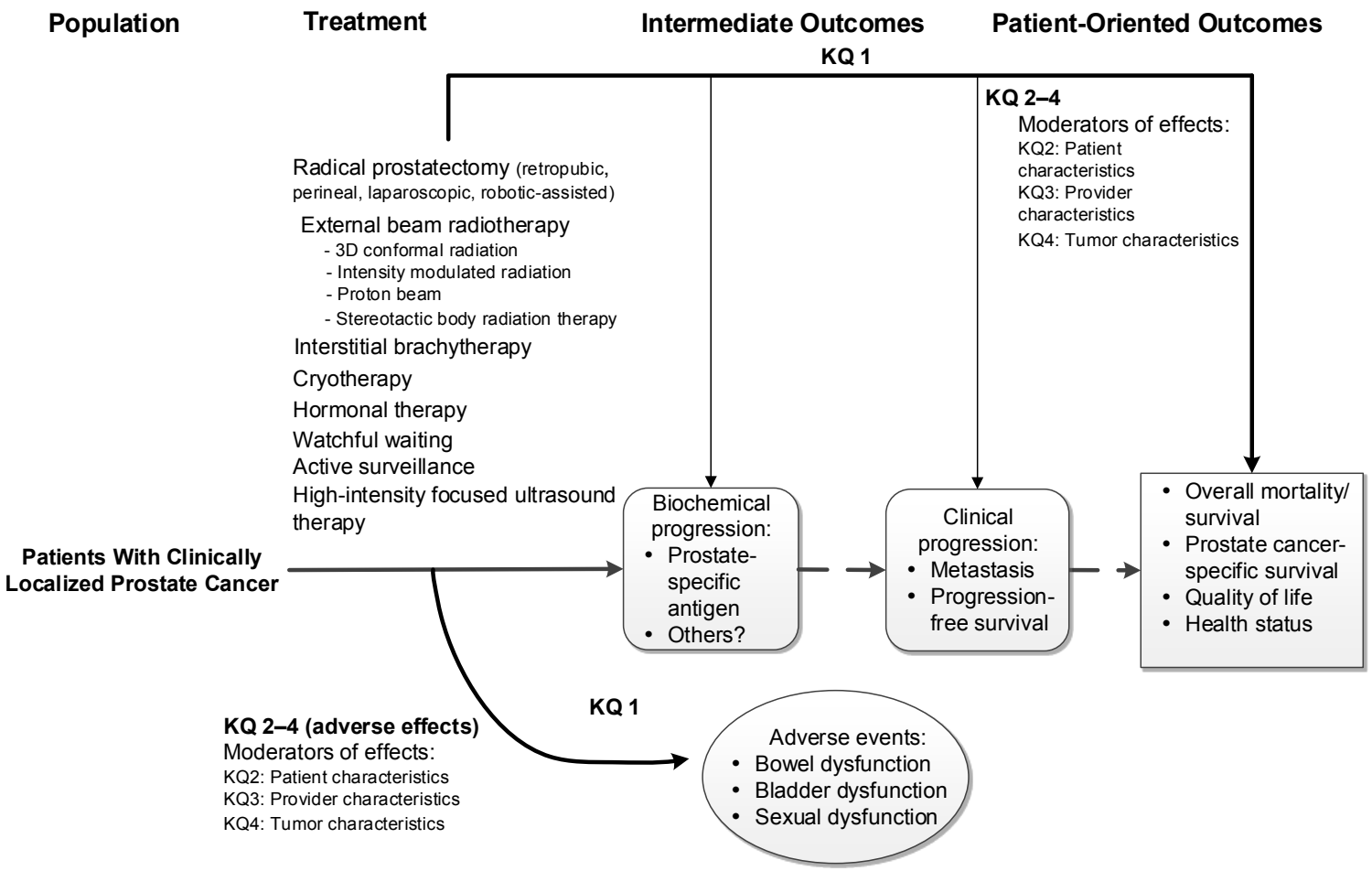
How do provider/hospital characteristics affect outcomes of these therapies overall and differentially (e.g., geographic region, case volume, learning curve)?

Key Question 4

How do tumor characteristics (e.g., Gleason score, tumor volume, screen-detected vs. clinically detected tumors, and PSA levels) affect the outcomes of these therapies overall and differentially?

II. Analytic Framework

Figure 1. Analytic Framework



3D, Three-dimensional; KQ: key question

Methods

This section documents the methods we used to conduct and produce this updated systematic review on therapies for clinically localized prostate cancer for the Agency for Healthcare Research and Quality (AHRQ) through its Effective Health Care Program (www.effectivehealthcare.ahrq.gov).

The methods used for preparing the 2008 comparative effectiveness review were developed through a rigorous process by the University of Minnesota Evidence-based Practice Center (EPC) in consultation with AHRQ and a technical expert panel (TEP).[13] We incorporated the methods from the original report where possible. However, for this update, our methods were informed by a more recent version of the guidance from the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews,"[48] hereafter referred to as the "Methods Guide." The search strategy was based on that composed for the 2008 report but we incorporated newer search methods and we reflected changes in the relevant nomenclature, such as differentiating active surveillance from watchful waiting. We used similar criteria and methods as in the 2008 report for study selection, data extraction, and risk-of-bias assessment for studies published since January 2007. The strength of evidence for each outcome was assessed according to more recent guidance from the "Methods Guide."[48]

Criteria for Inclusion and Exclusion of Studies for This Review Update

Study Design and Reporting Criteria

We used the same study selection criteria as in the 2008 report (see Table 6, Table 7, Table 8, and Table 9). For key questions (KQs) 1, 2, and 4, we included randomized trials only if the randomized treatment allocation was based on men with clinically localized disease and if clinical outcomes are reported for T1 and T2 disease separately from T3 and T4 disease. In the absence of any randomized trials, large nonrandomized comparative studies ($n \geq 500$) were considered for inclusion.

For KQ 3, we considered multicenter or comparative observational studies that examined the effect of provider characteristics on the diagnosis and treatment of localized prostate cancer.

Non-English–language studies were excluded. Moher et al.[52] have demonstrated that exclusion of non-English–language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.[53] found that non-English–language studies typically were of lower methodological quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English–language studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary to translate studies to identify those of acceptable quality for inclusion in our review.[52,53]

Table 6. Inclusion criteria: Key Question 1

Question Components	Inclusion Criteria
Major treatment options of interest: • Radical prostatectomy (retropubic, perineal, laparoscopic, robotic-assisted) • External beam radiotherapy • Interstitial brachytherapy • Hormonal therapy • Watchful waiting and active surveillance **Emerging treatment options of interest:** • Cryotherapy • High-intensity focused ultrasound therapy (Premarketing Approval Application for one device currently under consideration by the U.S. Food and Drug Administration) • Proton beam therapy • Stereotactic body radiation therapy **Outcomes of interest:** • Overall mortality and morbidity • Prostate-related mortality and morbidity • Quality of life • Adverse effects such as urinary incontinence and sexual dysfunction	RCTs comparing different treatment options that enrolled patients with clinically localized disease and reported outcomes of interest with duration of followup 1 year or more. Trials must focus on, or provide separate analyses for subjects with localized disease (T1/T2). RCTs that assigned treatments based on pathological staging (i.e., based on intraoperative findings) rather than clinical staging were excluded. When no RCTs were available, we considered large nonrandomized comparative studies (n≥500) that enrolled consecutive patients. For any nonrandomized comparative studies, we included only those that used an analytic method to address selection bias, such as intentional baseline matching on multiple characteristics, propensity scoring, or other analytic approach. The treatments being compared must have been administered during the same time period, so that any observed difference between outcomes were not attributable to differential time frames. For adverse events, we also included large nonrandomized comparative studies (n≥500) that reported relevant data. Studies could be prospective or retrospective; however, to reduce the risk of bias, retrospective studies must have used consecutive enrollment or enrollment of a random sample of eligible participants. Studies must have been published in English.

RCT=Randomized controlled trial.

Table 7. Inclusion criteria: Key Question 2

Question Components	Inclusion Criteria
Effectiveness outcomes according to patient age, race/ethnicity, comorbid conditions, and preferences	Studies that meet the inclusion criteria for Key Question 1 and report outcomes stratified according to patient characteristics

Table 8. Inclusion criteria: Key Question 3

Question Components	Inclusion Criteria
• Association between provider specialty and prostate cancer management • Association between physician characteristics and patient outcomes • Association between geographic region and outcomes • Association between hospital and provider case volume and outcomes	Studies using administrative data that measured outcomes in different locations, administrative surveys that measured physician distribution in U.S. regions, and epidemiologic studies that evaluated the association between provider characteristics and patient outcomes with a control group. Studies were excluded if there was no information regarding provider characteristics or if they were single-hospital studies with no control comparisons that did not test an associative hypothesis.

Table 9. Inclusion criteria: Key Question 4

Question Components	Inclusion Criteria
Effectiveness outcomes according to tumor characteristics (prostate-specific antigen, tumor stage, histologic grade, tumor risk strata)	Studies that meet the inclusion criteria for Key Question 1 and report outcomes stratified according to tumor characteristics

PICOTS Criteria

Population

- KQs 1, 2, 3, and 4: Men considered to have clinically localized prostate cancer (T1–T2, N0–X, M0–X) regardless of age, histologic grade, or prostate-specific antigen (PSA) level. Articles were excluded if men with disease stage higher than T2 were enrolled, and outcomes were not stratified by stage.

Interventions

- For KQs 1, 2, 3, and 4, we included treatment options for men with clinically localized prostate cancer: radical prostatectomy (including retropubic, perineal, laparoscopic, robotic-assisted), watchful waiting, active surveillance, external beam radiation therapy, including conventional radiation, intensity-modulated radiation therapy, three-dimensional conformal radiotherapy, proton beam, and stereotactic body radiation therapy), brachytherapy, hormonal therapy, high-intensity focused ultrasound, and cryotherapy.

Comparators

- Any of the interventions of interest above or watchful waiting.

Outcomes

- The primary outcome is overall mortality or survival. Additional outcomes include prostate cancer–specific mortality or survival, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, and quality of life. We focused primarily on common and severe adverse events of treatment including bowel, bladder, and sexual dysfunction, as well as harms from biopsy such as bleeding and nosocomial infections.
- For KQ 3, we planned to examine outcomes after radical prostatectomy, the most common treatment for localized prostate cancer, in association with provider location, case volume, and affiliation with academic centers.

Timing

- Duration of followup was appropriate for the outcome under consideration.

Settings

- No restrictions by setting.

Searching for the Evidence: Literature Search Strategies for Identifying Relevant Studies To Answer the Key Questions

Literature searches (see Table 10) were performed by medical librarians who followed established systematic search protocols. For all KQs, we searched the following databases on the OVID SP platform using the one-search and deduplication features: MEDLINE®, PreMEDLINE,

and EMBASE®. We also searched The Cochrane Library (including the Central Register of Controlled Trials, the Cochrane Database of Methodology Reviews, and the Cochrane Database of Systematic Reviews), the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, gray literature, and the U.K. National Health Service Economic Evaluation Database for unique reviews, trials, economic analyses, and technology assessments. We also used resources available through the EPC Scientific Resource Center to access Scientific Information Packets.

Search terms were identified by the following: (1) reviewing relevant systematic reviews on similar topics that are identified by the research staff; (2) reviewing how other relevant studies are indexed, their subject heading terms, and their keywords; and (3) reviewing MeSH® and EMTREE indexes for relevant and appropriate terms. We then identified a combination of subject headings and keywords and developed search strategies using these terms. Once developed, search strategies were reviewed by senior research analysts and senior medical librarians. A study-design filter was applied to retrieve systematic reviews and ongoing clinical trials. Details (specific search terms and search strategies) are provided in Appendix A of this protocol.

Table 10. Electronic database searches

Name	Platform/Provider
The Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Wiley
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Wiley
Cumulative Index of Nursing and Allied Health Literature (CINAHL®)	EBSCOhost
Database of Abstracts of Reviews of Effects (DARE)	Wiley
EMBASE® (Excerpta Medica)	OvidSP
Health Technology Assessment Database (HTA)	Wiley
MEDLINE®	OvidSP
PubMed® (In-process and publisher records)	National Library of Medicine
U.K. National Health Service Economic Evaluation Database (NHS EED)	Wiley
Gray Literature Resources	
ClinicalTrials.gov	National Institutes of Health
Centers for Disease Control and Prevention (CDC)	CDC
Centers for Medicare and Medicaid (CMS) - Medicare Coverage Database	CMS
Internet	Google
Manufacturers	Company name
Medscape	WebMD®
National Guideline Clearinghouse™ (NGC)	Agency for Healthcare Research and Quality
U.S. Food and Drug Administration (FDA), including Medical Device databases/Drugs@FDA	FDA

Note. The search period was from 2007 to the present in all databases.

The medical librarian initially reviewed the literature search results. Using the KQs and inclusion/exclusion criteria identified by senior research analysts, the medical librarian assessed

relevancy and retrieved results. Feedback from the senior research analysts and the senior medical librarian—including details regarding gaps in the search strategy and articles identified by the senior research analysts but not retrieved by the searches—were integrated into the search strategy using key terms and subject headings. The updated strategy was then reran in all identified databases. Additional results were scanned, and medical librarians assessed their relevancy. New results were downloaded and forwarded to senior research analysts for review. Hand searches of reference lists in identified articles were reviewed for possible inclusion. The search was updated during peer review of the draft report.

Articles were reviewed at the abstract level in duplicate, and any articles possibly meeting the inclusion criteria for at least one KQ was obtained for full review. When there were disagreements between both reviewers, a third reviewer resolved the issue.

Full articles was screened in duplicate, and any meeting the inclusion criteria was retained for abstraction of information on general study characteristics, patient characteristics, treatment characteristics, risk-of-bias items, and outcome data (see the next section).

A. Data Abstraction and Data Management

We used the DistillerSR® (Evidence Partners, Inc., Ottawa, Ontario, Canada) Web-based systematic review software for abstract screening and data extraction. Each team member's data extraction was reviewed by one other team member. Also, because of the possibility of subjective interpretation, the risk-of-bias items was judged in duplicate. We resolved all discrepancies through discussion. Two researchers extracted study, patient, tumor, and intervention characteristics and predefined outcomes onto standardized forms. Standard errors, regression coefficients, and 95 percent confidence interval (95% CI) was calculated from reported means, standard deviations, and sample size when provided/appropriate.[17] Multiple publications of the same study (e.g., publications reporting subgroups, other outcomes, longer followup) was identified by examining author affiliations, study designs, enrollment criteria, and enrollment dates.

B. Assessment of Methodological Risk of Bias of Individual Studies

As stated above, because of the possibility of subjective interpretation, assessment of methodological risk of bias of individual studies was performed by two researchers for each study, and discrepancies were resolved by consensus. When consensus could not be reached, a third researcher adjudicated. We assessed the risk of bias by following the guidelines in the chapter, "Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions" in the "Methods Guide."[18]

For KQs 1, 2, and 4, we assessed the risk of bias for the RCTs by evaluating several items such as such as randomization, allocation concealment, intention-to-treat-analysis, and completeness of followup (see Table 11). In addition, we assessed fidelity to the protocol to address performance bias and blinding of outcome assessors to address detection bias when outcomes are subjective (as defined in Table 11). Each of these items was answered "Yes," "No," or "Not reported."

Table 11. Risk of bias of included studies

Item	Comment
1. Were patients randomly assigned to the study groups?	—
2. Was there concealment of group allocation?	—
3. Were data analyzed based on the intention-to-treat-principle?	—
4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	—
5. Was the outcome measure of interest objective and was it objectively measured?	The following were considered objective outcomes: overall mortality or survival, prostate cancer–specific survival, adverse events, biochemical-free progression survival, hospital stay, and office visits. The following were considered subjective outcomes: quality of life and health status.
6. Was there a 15 percent or less difference in the length of followup for the two groups?	—
7. Did 85 percent or more of enrolled patients provide data at the time point of interest?	—
8. Was there fidelity to the protocol?	—

We categorized each study as having low, medium, or high risk of bias using the following method:

- To be considered as having low risk of bias, the study must meet all the following conditions:
  - There was randomization of study participants to treatment groups.
  - There was concealment of allocation.
  - Data analysis was based on the intention-to-treat-principle.
  - If outcome assessors were not blinded (item 4) or blinding of outcome assessors was not reported, then the outcome must have been objective (item 5).
  - There was a difference of 15 percent or less in the length of followup for the two groups.
  - Eighty-five percent or more of enrolled patients provided data at the time point of interest.
  - There was good fidelity to the protocol
- To be considered as having high risk of bias, the study must meet at least one of the following criteria:
  - The trial did not randomly assign patients to study groups and did not blind study outcome assessors.
  - The trial did not have a difference of 15 percent or less in the length of followup for the two groups.
  - The trial did not have good fidelity to the protocol.
- To be considered as having medium risk of bias, the study neither meets the criteria for low risk of bias nor the criteria for high risk of bias.

C. Data Synthesis

Because of the differences in study designs, treatments, patient and tumor characteristics, and reporting of outcomes, the 2008 report did not pool studies for KQs 1, 2, and 4. For the same reason, we performed only qualitative analysis in this update. Since RCTs and nonrandomized comparative studies differed substantially in average risk of bias, we performed separate qualitative analyses and present results separately for these study designs.

Study results were stratified based on study designs, comparisons across primary treatment categories, and comparisons within primary treatment categories.

Generally, we reported summaries of effectiveness and adverse-event outcomes with ranges according to treatment option, tumor characteristics, and group sample size. For KQ 1, we summarized and discussed comparative risks, benefits, and outcomes of therapies. For KQ 2, we summarized how patient characteristics affect outcomes. For KQ 4, we summarized how tumor characteristics affect outcomes.

D. Strength of the Body of Evidence

We provided evidence grades (see Table 12) for the following outcomes: overall mortality or survival, prostate cancer–specific survival, and quality of life. We assessed strength of evidence by following the guidelines from the publication, "Grading the Strength of a Body of Evidence When Comparing Medical Interventions," by Owens et al.[19] We graded the strength of evidence for each major health outcome based on the following dimensions:

- Risk of bias (low, medium, or high)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)

Two independent graders assessed each domain and differences were resolved by consensus.

The strength of evidence was allotted an overall grade of high, moderate, low, or insufficient as outlined in the publication by Owens et al. (see Table 12).[19] The decision to grade an evidence base as insufficient rather than low usually reflected an imprecise effect estimate (a non-statistically significant effect with 95% confidence intervals wide enough to allow the possibility of a significant benefit for one treatment compared to another) in an evidence base with only one or two studies. Evidence from a single study with medium or high risk of bias was also graded as Insufficient. When evidence came from subgroup analyses (KQ2 and KQ4), the strength of evidence was lowered by one level. For example, when the strength of evidence for a primary analysis in KQ1 was low, strength of evidence for subgroup analyses from the same studies was considered insufficient. This is because subgroup analyses were often not pre-specified in the study protocol, were often underpowered to detect differences between treatments, and generally should be considered as hypothesis-generating rather than definitive analyses.

Table 12. Strength-of-evidence grade for the body of evidence

Grade	Evidence-based Practice Center Program Definition
High	High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect.
Insufficient	Evidence is either unavailable or does not permit a conclusion.

Assessing the Applicability of the Evidence for Each Key Question

Applicability was assessed by following the guidelines in the publication, "Assessing the Applicability of Studies When Comparing Medical Interventions," by Atkins et al.[20] The applicability of the evidence involves the following five aspects: patients, interventions, comparisons, outcomes, and settings.[20] We addressed factors relevant to the applicability of the evidence by evaluating patient selection in both observational studies and clinical trials. We considered the primary biology and epidemiology (grade and stage of the prostate cancer) and the present-day clinical practice setting. The typical interventions, comparisons, outcomes (e.g., overall mortality, prostate cancer–specific survival), and settings of care were also used to more clearly specify the most applicable study characteristics (i.e., most typical of localized prostate cancer care in the United States).

Peer Review and Public Commentary

As part of a newly instituted process at AHRQ, the draft report will be reviewed before peer review by the Task Order Office (TOO) and an AHRQ associate editor (a senior member of another EPC). The revised draft report will be sent to invited peer reviewers and simultaneously uploaded to the AHRQ Web site where it will be available for public comment for 28 days. All reviewer comments (both invited and from the public) will be collated and individually addressed. The EPC responses to all comments will be documented in a disposition of comment document which will be posted on the Effective Health Care Web site about 3 months after Web publication of the evidence report. The authors of the report have final discretion as to how the report will be revised based on the reviewer comments, with oversight by the TOO and Associate Editor.

Results

In this chapter, the reader will find our literature search results, including information about how many abstracts we identified and why we excluded most abstracts from this report. This is followed by the key findings for key question (KQ) 1 (studies comparing different treatment options in patients with clinically localized prostate cancer) organized by treatment comparison (RCTs across primary treatment categories [3 unique studies describing 7 articles]), RCTs within primary treatment categories (4 unique studies describing 5 articles), and comparative outcomes data from nonrandomized studies (20 unique studies). A presentation of the findings for KQ 1 includes basic study design information, inclusion/exclusion criteria, outcomes reported, and a description of the instruments used to measure each outcome. This is followed by a more in-depth description of the study findings, a description of individual study risk of bias assessments, strength of evidence grades for the body of evidence, and applicability; all organized by the type of treatment comparisons studied. The same information is then provided for KQ 2 (study-reported outcomes stratified according to patient characteristics), and KQ 4 (study-reported outcomes stratified according to tumor characteristics), organized by treatment type.

Studies that addressed KQ1 reported data for patient-oriented outcome measures such as overall survival, all-cause mortality, prostate cancer-specific mortality, quality of life, and adverse events. None of the studies that addressed either KQ 2 or KQ 4 reported on adverse events based on patient subgroups (i.e., patient characteristics or tumor characteristics). All the studies that addressed either KQs 2 or KQ 4 only reported data for outcome measures such as overall survival, all-cause mortality, or prostate cancer-specific mortality. We did not identify any publications of interest that addressed KQ 3 (studies with information on provider/hospital characteristics that evaluated effect of the different treatment options in men with clinically localized prostate cancer). Table 13 and Table 14 provide an overview of the reported outcomes in the randomized controlled trials (RCTs) and nonrandomized comparative studies, respectively.

Literature Search Results

Our searches of the literature identified 3,081 potentially relevant articles. We excluded 816 articles by reviewing the titles, 2,126 by reviewing the abstracts, and 107 by reviewing the full-length articles. Figure 2 is a flow chart that describes in detail the exclusion process and the reasons for the exclusion at each review level.

The remaining 32 publications describing 27 unique studies made up the evidence base for this review. Thirty-two articles describing 27 unique studies addressed KQ 1, 6 studies addressed KQ 2, and 8 studies addressed KQ 4.

Figure 2. Literature flow diagram

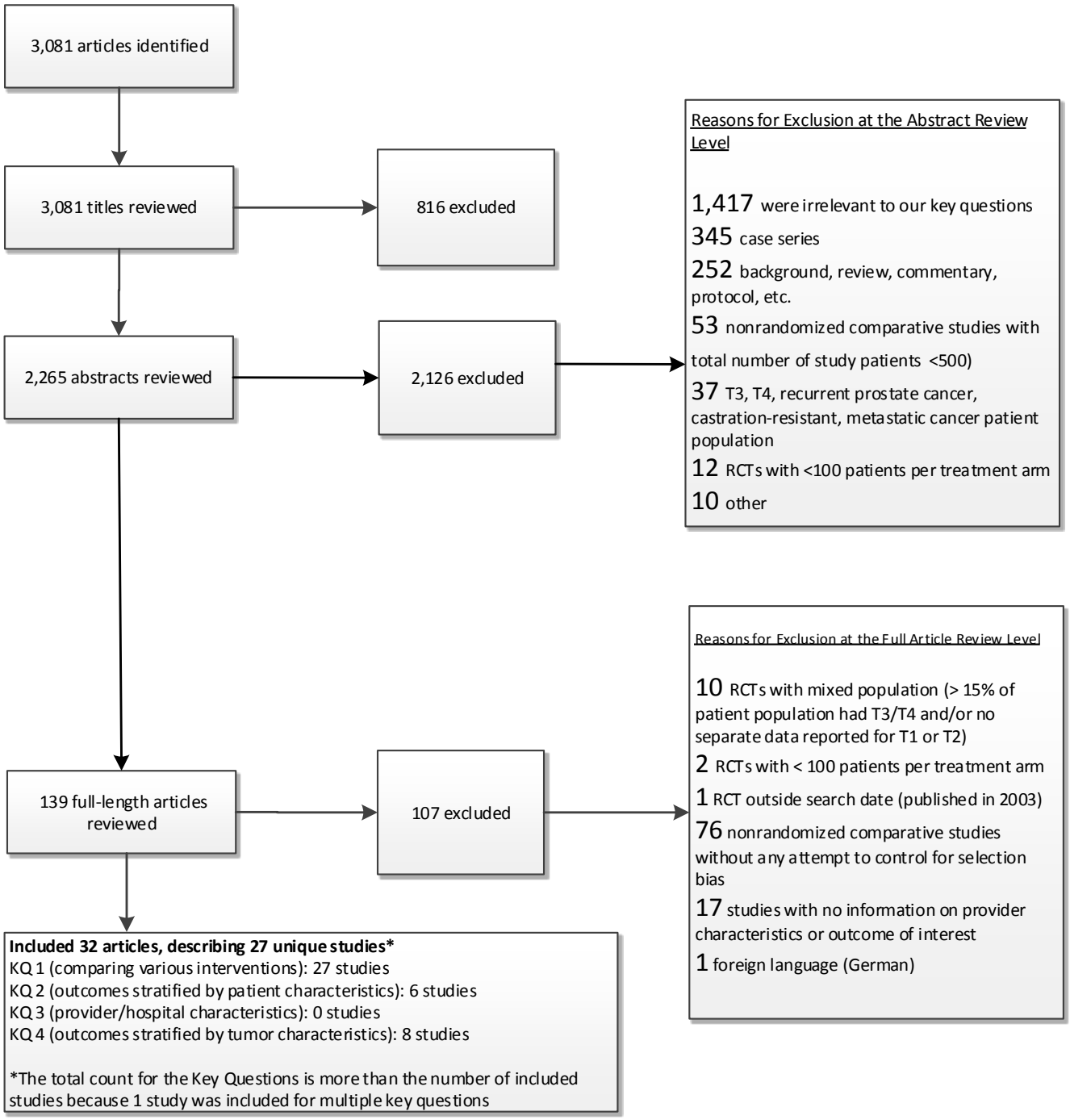


Table 13. Reported outcomes for randomized controlled trials

Study	Comparison	Overall Survival	All-cause Mortality	Prostate Cancer–specific Mortality	Quality of Life	Biochemical Progression	Clinical Progression	Adverse Events
Wilt et al. 2012[16] Prostate Intervention vs. Observation Trial (PIVOT)	RP vs. observation		✓	✓			✓	✓
Bill-Axelson et al. 2011[25] Same study as Johansson et al. 2011,[47] Holmberg et al. 2012,[54] and Bill-Axelson et al., 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) trial	RP vs. watchful waiting		✓	✓	✓		✓	✓
Giberti et al. 2009[21]	RRP vs. brachytherapy				✓	✓		✓
Jones et al. 2011[26]	EBRT vs. EBRT plus short-term ADT	✓		✓	✓	✓	✓	✓
Widmark et al. 2009[23]	ADT vs. ADT plus EBRT			✓				
D'Amico et al. 2008[24]	EBRT vs. EBRT plus ADT		✓	✓				
Martis et al. 2007[22]	RRP vs. radical perineal prostatectomy							✓

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy.

Table 14. Reported outcomes for nonrandomized comparative studies

Study	Comparison	Overall Survival	All-cause Mortality	Prostate Cancer–specific Mortality	Quality of Life	Biochemical Progression	Clinical Progression	Adverse Events
Resnick et al., 2013[44]	RP vs. radiotherapy				✓			
Abdollah et al., 2012[32]	Radiotherapy vs. observation			✓				
Barry et al., 2012[35]	RALP vs. open RRP							✓
Kibel et al., 2012[31]	RP vs. 3D-CRT plus IMRT vs. BT	✓		✓				

Table 14. Reported outcomes for nonrandomized comparative studies (continued)

Study	Comparison	Overall Survival	All-cause Mortality	Prostate Cancer–specific Mortality	Quality of Life	Biochemical Progression	Clinical Progression	Adverse Events
Mohammed et al., 2012[39]	BT vs. image-guided radiation therapy-EBRT vs. high dose-rate-EBRT							✓
Rosenberg et al., 2012[33]	BT plus EBRT vs. BT plus ADT			✓				
Sheets et al., 2012[45]	IMRT vs. 3D-CRT vs. proton beam therapy							✓
Shen et al., 2012[42]	BT vs. BT plus EBRT vs. EBRT			✓				
Abdollah et al., 2011[49]	RP vs. observation		✓	✓				
Bekelman et al., 2011[40]	IMRT vs. 3D-CRT							✓
Williams et al., 2011[37]	BT vs. cryotherapy							✓
Hadley et al., 2010[38]	RP vs. conservative management		✓	✓				
Barocas et al., 2010[27]	RRP vs. RALP					✓		
Malcolm et al., 2009[34]	Open radical prostatectomy vs. robotic-assisted prostatectomy vs. BT vs. cryotherapy				✓			
Dosoretz et al., 2010[41]	BT vs. BT plus ADT		✓					
Krambeck et al., 2008[28]	RRP vs. RALP		✓	✓	✓	✓	✓	
Lu-Yao et al., 2008[36]	Primary ADT vs. conservative management	✓		✓				
Schroeck et al., 2008[29]	RRP vs. RALP					✓		
Albertsen et al., 2007[43]	Surgery vs. radiation	✓		✓				
Ferrer et al., 2008[30]	RP vs. 3D-CRT vs. BT				✓			

3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; BT=brachytherapy; EBRT=external beam radiation therapy; IMRT=intensity-modulated radiation therapy; RALP=robotic-assisted laparoscopic prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy.

Key Question 1. What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?

a. Radical prostatectomy (RP), including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches
b. EBRT, including standard therapy and therapies designed to decrease exposure to normal tissues such as three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), proton beam therapy, and stereotactic body radiation therapy
c. Interstitial brachytherapy (BT)
d. Cryotherapy
e. Watchful waiting (WW)
f. Active surveillance
g. Hormonal therapy
h. High-intensity focused ultrasound

The main treatment options for clinically localized prostate cancer are identified and summarized in Table 5. In this section, we summarize findings from RCTs and describe additional data from the nonrandomized comparative studies. Table 15 compares major primary treatment options and reports clinical outcome measures for the randomized controlled trials across primary treatment categories. Table 16 compares major primary treatment options and reports clinical outcome measures for the randomized controlled trials within primary treatment categories. Table 17 compares major primary treatment options and reports clinical outcome measures for the nonrandomized comparative studies.

Results by Comparison

Randomized Controlled Trials

Study Characteristics

General information including baseline demographic and tumor characteristics about the 7 RCTs in 12 unique studies included for this KQ appears in Table 50 of Appendix F. The seven RCTs included a total of 4,886 men at enrollment (1,011 underwent RP, 1,096 received EBRT alone, 1,525 received EBRT plus androgen-deprivation therapy [ADT], 100 received BT, 439 received ADT alone, and 715 managed by observation or WW). The RCTs enrolled between 200 and 1,979 patients each. The dates of patient enrollment were reported by all of the seven studies. The range of average length of the enrollment period was 7 years (range 3.5–10.0 years). Four studies reported age with an average of 74.8 (range 71–76).

Two studies each were conducted in the United States[16,24] and Italy[21,22]; and the rest were conducted in multiple countries (U.S. and Canada[26]; Sweden, Finland, and Iceland[46]; and Sweden, Norway, and Denmark[23]). Four were multicenter RCTs[16,23,26,46] including one study[26] which was a phase III study and three[21,22,24] were single-center RCTs.

Regarding specific treatment interventions, the most commonly compared procedures were RP versus observation or watchful waiting (2 studies)[16,25] and EBRT versus EBRT plus ADT (2 studies).[24,26] The remaining three studies compared radical retropubic prostatectomy versus BT,[21] ADT versus ADT plus EBRT,[23] and retropubic versus perineal prostatectomy.[22]

Although none of the included RCTs provided details of expertise of the participating surgeons, surgical technique varied across these studies. One study[25] reported radical excision of the tumor was given priority over nerve-sparing, one study[16] reported surgical technique was at the discretion of the surgeon, and two studies[21,22] each reported a bilateral nerve sparing technique was performed on all patients by a single surgeon. Radiation therapy also varied among the included studies. In one study[26] radiotherapy was administered in daily 1.8 Gray (Gy) fractions, with 46.8 Gy delivered to the prostate and regional lymph nodes, followed by 19.8 Gy to the prostate. Another study[23] administered a radiation dose of 50 Gy to the prostate and seminal vesicle, followed by a sequential boost of at least 20 Gy to the prostate, making a total dose minimum of 70 Gy. One study[21] administered BT using a transperineal template-guided peripheral loading real-time technique and seeds of iodine 125. ADT also varied among included studies. One study[26] reported flutamide (250 mg) was administered and another study[24] did not report the specific dose of the flutamide. Patient enrollment criteria and description of treatment details appear in Table 48 of Appendix E.

The population for six included studies was patients with T1 and T2 prostate cancer.[16,21,22,24,26,46] For one study,[23] the population was patients with T1, T2, or T3 prostate cancer, however, this study reported separate data for patients with T1–T2 prostate cancer. Four studies[21-24] reported patient exclusion criteria.

Baseline clinical tumor staging data were reported for all studies. One study[23] did not report biopsy Gleason grade or score. Three studies reported mean Gleason scores[16,21,22] and three reported Gleason scores range only.[24-26]

All the RCTs gave preoperative prostate-specific antigen (PSA) levels for each group of men. Four studies reported mean and median PSA,[16,21-23] one study reported mean PSA,[46] one study reported median PSA,[24] and one study reported PSA range only.[26]

Three studies had an outcome measure of all-cause mortality,[16,24,25] five studies had an outcome measure of prostate cancer–specific mortality,[16,23,24,26,46] two studies had an outcome measure of overall survival,[24,26] three studies had an outcome measure of quality of life (QOL),[21,26,46] four studies reported on adverse events,[16,22,26,46] three studies had an outcome measure of distant metastases,[16,26,46] and one study reported on each biochemical disease-free survival[21] and biochemical failure.[26] (See Table 15 and Table 16.)

Table 15. Overview of randomized controlled trials across primary treatment categories (3 trials): Key Question 1

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Wilt et al. 2012[16] Prostate Intervention vs. Observation Trial (PIVOT)	RP (364 patients) vs. observation (367 patients)	Age 75 years or younger, T1-T2NxM0, PSA <50 ng/mL	All-cause mortality Prostate cancer–specific mortality (PCSM) Distant metastases Adverse events	Median followup of 10 years

Table15. Overview of randomized controlled trials across primary treatment categories (3 trials): Key Question 1 (continued)

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Bill-Axelson et al. 2011[25] Same study as Johansson et al., 2011,[47] Holmberg et al., 2012,[54] and Bill-Axelson et al., 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) trial	RP (347 patients) vs. watchful waiting (348 patients)	Age 77 years or younger, T1b, T1c, T2, PSA <50 ng/mL	Overall mortality PCSM Distant metastases Adverse events Quality of life (QOL)	Median followup of 15 years
Giberti et al. 2009[21]	RRP (100 patients) vs. brachytherapy using iodine 125 (100 patients)	Caucasian men, T1c or T2a, PSA value ≤10 ng/mL and Gleason sum ≤6)	Biochemical disease-free survival QOL Adverse events	Followup of 5 years

PCSM=Prostate cancer–specific mortality; PSA=prostate-specific antigen; QOL=quality of life; RP=radical prostatectomy; RRP=radical retropubic prostatectomy.

Table 16. Overview of randomized controlled trials within primary treatment categories (4 trials): Key Question 1

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Jones et al. 2011[26]	EBRT (992 patients) vs. EBRT plus short-term ADT (987 patients)	Age 71 years or younger, T1b, T1c, T2a, T2b prostate adenocarcinoma, PSA ≤20 ng/mL	Overall survival Prostate cancer-specific mortality (PCSM) Biochemical failure Distant metastases Quality of life (QOL) Adverse events	Median followup of 9.1 years
Widmark et al. 2009[23]	ADT (439 patients) vs. ADT plus EBRT (436 patients)	Age 76 years or younger, T1, T2, T3 PSA <70 ng/mL	*PCSM	Median followup of 7.6 years
D'Amico et al. 2008[24]	EBRT: (104 patients) vs. EBRT plus ADT (102 patients)	T1, T2 patients who had at least a 10-year life expectancy excluding death from prostate cancer	Overall survival All-cause mortality PCSM	Median followup of 7.6 years
Martis et al. 2007[22]	Radical retropubic prostatectomy (100 patients) vs. radical perineal prostatectomy (100 patients)	T1, T2	Adverse events	Followup of 2 years

* This was the only outcome that was reported separately for patients with T1b to T2 cancer.

ADT=Androgen deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PSA=prostate-specific antigen; QOL=quality of life.

Risk of Bias

Our risk-of-bias assessments for the seven studies appear in Table 46 of Appendix D. Three studies[16,21,22] were categorized as medium risk of bias for all of their reported outcomes. Two studies[23,24] were categorized as low risk of bias for all of their reported outcomes. One study[25] was categorized as low risk of bias for all outcomes except for QOL that was rated medium risk of bias. One study[26] was categorized as medium risk of bias for all outcomes except for QOL that was rated high risk of bias. Common reasons for assigning a medium category to the studies were lack of concealment of allocation and lack of outcome assessor blinding. Assignment of high risk of bias occurred when a subjective outcome such as QOL was assessed in a study with lack of concealment of allocation and lack of outcome assessor blinding.

Findings

All abstracted data for the outcome measures that address this KQ appear in Table 52, Table 54, Table 56, Table 58, Table 60, Table 62, Table 64, and Table 66 of Appendix G.

Efficacy and Adverse Events Outcomes

Randomized Controlled Trials - Comparisons Across Primary Treatment Categories

A. Radical Prostatectomy Versus Watchful Waiting (Two RCTs in Four Unique Studies)[16,25,46,54]

All-Cause Mortality

Wilt et al.[16] in the Prostate Cancer Intervention Versus Observation Trial (PIVOT) reported they found no reduction in all-cause mortality among men with T1–T2NxM0 prostate cancer that were treated with RP compared with WW. At a median followup of 10.0 years, 47 percent (171/364) of men in the RP treatment group died, compared with 49.9 percent (183/367) in the WW group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.71 to 1.08; p=0.22; absolute risk reduction [ARR], 2.9 percent; 95% CI, -4.1 to 10.3). The median survival was 13.0 years (95% CI, 12.2 to 13.7) in the RP group and 12.4 years (95% CI, 11.4 to 13.1) in the WW group. By 12 years after treatment, 40.9 percent of men in the RP group had died compared with 43.9 percent who died in the WW group. The absolute reduction in mortality following RP, however, declined from 4.6 percent (95% CI, -0.2 to 9.3) at 4 years to 2.9 percent (95% CI, -4.2 to 10.0) at 12 years. Overall, RP did not considerably reduce all-cause mortality compared with WW.

Bill-Axelson et al.[25,46,54] in the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial reported estimated 12- and 15-year results. Of the 695 men with T1b, T1c, or T2 included in the study, 47.8 percent (166/347) of men in the RP treatment group died, compared with 57.8 percent (201/348) in the WW group during a median followup of 12.8 years (p=0.007). Overall mortality at 12-year followup was 32.7 percent in the RP group and 39.8 percent in the WW group (difference 7.1 percent; 95% CI, -0.5 to 14.7%), corresponding to a risk ratio (RR) 0.82 (95% CI, 0.65 to 1.03, p=0.09). The cumulative incidence of deaths at 15 years was 46.1 percent in the RP group and 52.7 percent in the WW group (difference of 6.6 percent; 95% CI, -1.3 to 14.5) equivalent to a relative risk (RR) of death in the RP group of 0.75 (95% CI, 0.61 to 0.92;

p=0.007) and a number needed to treat of 15. One death was reported in the RP group during the postoperative period.

We did not combine both studies because the PIVOT[16] and SPCG-4[25] enrolled different populations. In comparison to the SPCG-4 trial, the PIVOT study enrolled a higher percentage of men with nonpalpable tumors and low PSA values. The SPCG-4 trial began in 1989 when PSA screening was not widespread. Although the trial's eligibility criteria was T1 or T2, these tumors were at risk of being understaged compared with tumor staging in the cohort in PIVOT. Following RP, nearly half of the patients in the SPCG-4 trial compared with about 15 percent of patients in the PIVOT study had extracapsular extension (pT3, tumor extending beyond capsule). Additionally, the protocol for the WW arms differed between these studies. In the SPCG-4 trial, transurethral resection of the prostate (TURP) was recommended as the initial treatment for men with urinary obstruction, and hormonal treatment was recommended for men with disseminated disease (before January 2003) or as the patient's physician advised it (after January 2003). In the PIVOT study, patients with symptomatic local progression are treated first with alpha blockers or mechanical intervention (e.g., TURP). Hormonal therapy is considered first-line therapy for patients with disease progression requiring nonmechanical therapy. Patients with disease that continued to progress or failed to respond to hormonal therapy underwent radiotherapy or chemotherapy. In the PIVOT study, patients with symptomatic local disease progression despite mechanical therapy and alpha blockers may also undergo prostatectomy.

Prostate Cancer–Specific Mortality

The number of men who died from prostate cancer varied widely across both studies. In the PIVOT study,[16] 21 men (5.8 percent) died in the RP group compared with 31 men (8.4 percent) in the WW group (HR, 0.63; 95% CI, 0.36 to 1.09; p=0.09; ARR 2.6 percent; 95% CI, -1.1 to 6.5). However, at 4-year followup, prostate cancer–specific mortality was comparable between both study groups. The absolute reduction of 3.0 percent in the RP group was not substantial compared with WW (4.4 percent vs. 7.4 percent, RR, 0.60; 95% CI, 0.33 to 1.09) at the 12-year followup.

In the SPCG-4 study,[25,46,54] a higher rate of death due to prostate cancer was reported at 12- and 15-year followup periods in the WW group. At the 12-year period, 13.5 percent (47/347) of men in the RP and 19.5 percent (68/348) of men in the WW group had died due to prostate cancer. By the 15-year followup period, 55 deaths (15.9 percent) due to prostate cancer were reported in the RP group compared with 81 deaths (23.3 percent) in the WW group.[25,46,54] At the 12-year followup period, the cumulative incidence of prostate cancer–specific mortality was 12.5 percent of men in the RP compared with 17.9 percent in the WW group (difference 5.4 percent; 95% CI, 0.2 to 11.1), with an RR of 0.65 (95% CI, 0.45 to 0.94; p=0.03). At 15-year followup, the cumulative incidence of deaths was 14.6 percent in the RP group and 20.7 percent in the WW group (difference of 6.1 percent, 95% CI, 0.2 to 12.0), with RR of death in the RP group of 0.62 (95% CI, 0.44 to 0.87; p=0.01).

We did not combine both studies for the same reasons reported above.

Distant Metastases

Wilt et al.[16] reported metastatic bone lesions in 17 men (4.7 percent) in the RP group and 39 men (10 percent) in the WW group (HR, 0.40; 95% CI, 0.22 to 0.70; p<0.001). There was minimal change in the differences in the cumulative incidence between both study groups after the 8-year followup period.

Bill-Axelson et al.[25,46,54] reported distant metastases in 67 of 347 men (19.3 percent) in the RP group and 96 of 348 men (27.6 percent) in the WW group (difference 6.7 percent; 95% CI, 0.2 to 13.2 percent), for a RR of 0.65 (95% CI, 0.47 to 0.88; p=0.006). At 15-year followup, the number of men with distant metastases had increased to 81 (23.3 percent) in the RP group and 123 (35.3 percent) in the WW group. The cumulative incidence at 15 years was 21.7 percent in the RP group and 33.4 percent in the WW group (difference of 11.7 percent; 95% CI, 4.8 to 18.6), corresponding to an RR of distant metastases in the RP group of 0.59 (95% CI, 0.45 to 0.79; p<0.001).

Quality of Life

Long-term quality of life (QOL) was reported by some men at two followup points 9 years apart in the SPCG-4 study.[47] At a median followup of 12.2 years (range 7-17), high self-assessed QOL was reported in 35 percent (62/179) of men in the RP group and 34 percent (55/160) in the WW group (RR 0.98; 95% CI, 0.73 to 1.31). The authors also reported intensity of psychological symptoms. Results were as follows:

- Men who described moderate or high anxiety were 43 percent (77/178) in the RP group versus 43 percent (69/161) in the WW group; RR 0.97; 95% CI, 0.76 to 1.24)
- Men who described moderate or high depressed mood were 47 percent (85/180) in the RP group versus 52 percent (82/159) in the WW group; RR 0.92; 95% CI, 0.74 to 1.14)
- Men who described high well-being were 41 percent (73/179) in the RP group versus 44 percent (71/161) in the WW group; RR 0.89; 95% CI, 0.70 to 1.13)
- Men who described a high sense of meaningfulness were 46 percent (83/179) in the RP group versus 49 percent (79/160) in the WW group; RR 0.92; 95% CI, 0.74 to 1.15)

Adverse Events

Wilt et al.[16] reported adverse events in 21.4 percent of 364 men, including 1 death within 30 days after RP. The most commonly reported adverse event was wound infection in 4.3 percent of men. Other adverse events that were reported in fewer than 2 percent of men included surgical repair, urinary tract infection, bleeding requiring blood transfusion, and urinary catheterization more than 1 month postoperatively. At 2-year followup, more men in the RP group compared with WW reported erectile dysfunction (231/285, 81.1 percent vs. 124/281, 44.1 percent) and urinary incontinence (49/287, 17.1 percent vs. 18/284, 6.3 percent). Patient-reported bowel dysfunction, however, was comparable in both groups (35/286, 12.2 percent vs. 32/282, 11.3 percent).

Bill-Axelson et al.[47] reported data in a total of 289 men within 1 year after RP as number of events and 1-year cumulative incidence (95% CI; 1 man died postoperatively):

- Urinary leakage, 93 events, 32.2 (27.2–38.1) 1-year cumulative incidence
- Urinary obstruction 6 events, 2.1 (0.9–4.6) 1-year cumulative incidence
- Impotence 168 events, 58.1 (52.7–64.1) 1-year cumulative incidence
- Pulmonary embolism 4 events, 1.4 (0.5–3.7) 1-year cumulative incidence
- Deep vein thrombosis 3 events, 1.0 (0.3–3.2) 1-year cumulative incidence

At the 4-year followup period, the prevalence of erectile dysfunction and urinary leakage was greater after RP than with WW (erectile dysfunction was 80 percent in the RP vs. 45 percent in the WW group, urinary leakage 49 percent in the RP vs. 21 percent in the WW group).[54]

B. Radical Retropubic Prostatectomy Versus Brachytherapy (One RCT)[21]

Biochemical Disease-Free Survival

Giberti et al.[21] reported and compared biochemical disease-free survival rates between radical retropubic prostatectomy (RRP) and BT which was performed using a transperineal template-guided peripheral loading real-time technique and seeds of iodine 125. At 5-year followup, the rates of biochemical disease-free survival were comparable at 91.0 percent (81/89 patients) and 91.8 percent (78/85 patients), respectively.

Quality of Life

The authors also reported QOL data measured by the European Organization for research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)-C30 and found a deterioration of physical and emotional functions in both groups at the 1-year followup period.[21] No differences were found in either the physical or emotional functions after 5-year followup.

Adverse Events

At 6-month followup, 18.4 percent of men in the RRP group reported urinary incontinence (severe in 5.4 percent and mild in 13.0 percent). In the BT group, urinary irritation was reported by 80 percent and 20 percent of men at the 6-month and 1-year followup periods, respectively.[21] Proctitis was also reported among men in the BT group at 6-month followup. With reference to erectile function, both groups reported falling scores on both the QLQ-PR25 and International Index of Erectile Function at 6-month followup. However, these scores improved by the 1-year followup.[21] No difference was found in erectile function and urinary disorders at the 5-year followup period in either study group.

Randomized Controlled Trials – Comparisons Within Primary Treatment Categories

A. External Beam Radiotherapy Versus External Beam Radiotherapy Plus Androgen-Deprivation Therapy (Two RCTs)[24,26]

Overall Survival

Two studies reported that overall survival was higher for men in the EBRT plus ADT group compared with overall survival with EBRT alone. A phase III trial by Jones et al.[26] included low-risk prostate cancer patients and reported that the 10-year rate of overall survival among men with T1b, T1c, T2a, or T2b prostate cancer was increased to 62 percent in the EBRT plus short-term ADT group compared with 57 percent in the EBRT alone group (HR for death with EBRT alone, 1.17; 95% CI, 1.01 to 1.35; p=0.03). The study administered EBRT in daily 1.8 Gy fractions of 46.8 Gy delivered to the pelvis, followed by 19.8 Gy to the prostate, for a total dose of 66.6 Gy. Short-term ADT included flutamide at a dosage of 250 mg three times a day and monthly goserelin at a dosage of 3.6 mg or leuprolide at a dose of 7.5 mg for 4 months.

In the second study, D'Amico et al.[24] enrolled intermediate-risk prostate cancer patients or "localized but unfavorable characteristics." The Kaplan-Meier 8-year survival estimates among men with T1 or T2 prostate cancer who had at least a 10-year life expectancy excluding death

from prostate cancer was 74 percent (95% CI, 64 percent to 82 percent) in the EBRT plus 6 months of ADT group compared with 61 percent (95%, CI, 49 percent to 71 percent) in the EBRT-alone group, p=0.01. The study administered a daily EBRT dose of 1.8 Gy for initial 25 treatments, totaling 45 Gy, and 2.0 Gy for final 11 treatments, totaling 22 Gy. Six months of ADT was comprised of both of the following:

- Leuprolide each month at a dose of 7.5 mg or 22.5 mg every 3 months or goserelin 3.6 mg or 10.8 mg every 3 months
- Flutamide 250 mg every 8 hours and starting 1 to 3 days before the leuprolide

All-Cause Mortality

D'Amico et al.[24] reported an increase in the risk of all-cause mortality (44 vs. 30 deaths; HR, 1.8; 95% CI, 1.1 to 2.9; p=0.01) in the EBRT group compared with the EBRT plus 6 months of ADT.

Prostate Cancer–Specific Mortality

Both studies reported a reduction in the prostate cancer–specific mortality among the men who received EBRT plus ADT compared with EBRT alone. Jones et al.[26] reported a decrease from 8 percent in the EBRT alone group to 4 percent in the EBRT plus short-term ADT group (HR for EBRT alone, 1.87; 95% CI, 1.27 to 2.74; p=0.001). Of all the 74 deaths reported by D'Amico et al.,[24] 18 were due to prostate cancer and, of these, 4 occurred in men who received EBRT plus 6 months of ADT and 14 occurred in men who received EBRT alone.

Biochemical Failure

The 10-year rate of biochemical failure reported by Jones et al.[26] was reduced to 26 percent in the EBRT plus short-term ADT group from 41 percent in the EBRT alone group (HR, 1.74; 95% CI, 1.48 to 2.04; p<0.001).

Distant Metastases

The 10-year cumulative incidence of distant metastases reported by Jones et al.[26] was reduced to 6 percent in the EBRT plus short-term ADT group from 8 percent in the EBRT alone group (HR, 1.45; 95% CI, 1.03 to 2.06; p=0.04).

Quality of Life

At 1 year, 85 men (35 percent) in the EBRT alone group compared with 59 men (21 percent) in the EBRT plus short-term ADT group reported always/almost always [effect of short-term ADT on erectile function] on the Sexual Adjustment Questionnaire (p=0.004) in the study by Jones et al.[26]

Adverse Events

Jones et al.[26] reported the men in the EBRT alone group had an increased incidence of grade 3 or higher acute and late gastrointestinal toxicity (EBRT 3 percent vs. EBRT plus short-term ADT 1 percent) occurring up to 90 days after the start of EBRT.

B. Androgen-Deprivation Therapy Versus Androgen-Deprivation Therapy Plus External Beam Radiotherapy (one RCT)[23]*

Prostate Cancer–Specific Mortality

Widmark et al.[23] included men who had T1b–T2 and T3 prostate cancer; only the data on men with T1b-T2 stage cancer met our inclusion criteria. Subgroup analysis stratified by T stage showed a reduction in the 10-year cumulative incidence of prostate cancer–specific mortality. This observed reduction was apparent among men with T1b–T2 prostate cancer who received 3 months of ADT plus EBRT compared with ADT alone (mean ARR 16.0; 95% CI, 3.7 to 28.2). ADT treatment included leuprolide 3.75 mg a month or 11.25 mg every 3 months and flutamide. Flutamide was replaced with 150 mg of bicalutamide once daily when side effects occurred. After 3 months of total androgen blockade, patients continued using flutamide until progression or death. The EBRT comprised of a central dose of 50 Gy to the prostate and seminal vesicle, followed by a sequential boost at least 20 Gy to the prostate.

C. Radical Perineal Prostatectomy Versus Radical Retropubic Prostatectomy (one RCT)[22]

Prostate Cancer–Specific Mortality

Martis et al.[22] reported data on adverse events at 6 and 24 months in men with T1a, T2a, or T2b prostate cancer. Urinary continence at 6-month followup was reported in 74 men (74 percent) in the perineal group versus 76 men (76 percent) in the retropubic prostatectomy group and at 24-month followup was reported in 96 men (96 percent) in the perineal group versus 95 men (95 percent) in the retropubic prostatectomy group. Erectile function at 6-month followup was reported in 30 men (30 percent) in the perineal group versus 45 men (45 percent) in the retropubic prostatectomy group and at 24-month followup was reported in 42 men (42 percent) in the perineal group versus 60 men (60 percent) in the retropubic prostatectomy group. The study authors concluded that radical perineal prostatectomy is an effective substitute for radical retropubic prostatectomy.

Nonrandomized Comparative Studies

Study Characteristics

General information including baseline demographic and tumor characteristics of the 20 nonrandomized comparative studies (of 500 or more patients) that addressed this KQ appears in Table 51 of Appendix F. The 20 nonrandomized comparative studies included a total of 206,922 men at enrollment. However, because 10 of the 20 studies drew their sample from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database, the number of unique study participants presented here is greatly inflated. Of the 206,922 men enrolled (35,414 underwent RP, 87,237 received EBRT alone, 14,780 received BT, 7,867 received ADT alone, 1,024 received cryotherapy alone, 4,356 received combination therapy, and 56,244 were managed by observation). The 20 nonrandomized comparative studies enrolled between 614 and 68,797 patients each. The duration of patient followup across the studies ranged from 14 months to 15 years. Nine studies reported the median age of participants and five studies each reported patient age in mean years or categorically. The median patient age reported ranged

from 59.2 years to 79 years. Nineteen of the 20 studies were conducted in the United States and 1 was conducted in Spain.[30]

Regarding specific treatment interventions, the most commonly compared procedures were robotic radical prostatectomy versus radical retropubic prostatectomy (3 studies).[27-29] The remaining studies compared the following:

- RP versus three-dimensional conformal radiation therapy (3D-CRT) versus BT[30]
- RP versus EBRT (3D-CRT or IMRT) versus BT[31]
- RP versus EBRT[44]
- RP versus observation[49]
- BT plus EBRT versus BT plus ADT[33]
- Open radical prostatectomy versus robotic radical prostatectomy versus cryotherapy versus BT[34]
- Robotic prostatectomy versus open retropubic prostatectomy[35]
- Conservative management versus ADT[36]
- Conservative management versus RP[38]
- BT versus cryotherapy[37]
- BT versus image guided-EBRT versus high-dose-rate EBRT[39]
- IMRT versus 3D-CRT[40]
- IMRT versus proton beam therapy versus 3D-CRT[45]
- BT versus BT plus ADT[41]
- BT versus EBRT versus BT plus EBRT[42]
- Observation versus radiotherapy[32]
- RP versus EBRT versus observation[43]

A great deal of variability existed in the level of detail provided on treatment techniques in the nonrandomized trials. Five trials described RP as robot-assisted,[27-29,34,35] and in a sixth study,[31] the procedure was either retropubic or laparoscopic. Malcolm et al.[34] specified that robotic-assisted laparoscopic prostatectomy used nerve sparing techniques and Schroeck et al.[29] reported that the Vattikuti Institute technique was followed. The retropubic technique was used in at least one treatment arm by four studies[27,28,28,29,35] and was either retropubic or perineal, with nerve-sparing techniques, in another study.[34] The only study to describe how cryotherapy was delivered reported that it was delivered with a third-generation delivery system.[34] BT was delivered using a variety of methods including intraoperative treatment planning with ultrasound guidance with a median dose of 14,400 to 14,500 cGy,[31] either a high-dose or low-dose rate,[39] iodine 125 or palladium 103,[41] and with a modified peripheral loading dose rate technique with permanent palladium seeds delivering an average of 125 Gy dose.[34] EBRT was delivered at a median dose of 7,400 to 7,800 cGy in the one study that provided detail.[31] One study evaluated methods for addressing confounding in treatment and survival of patients with early-stage prostate cancer in observational data and compared findings with those from a benchmark RCT.[38] Study selection criteria and description of treatment appear in Table 49 of Appendix E.

The percentage of patients with a clinical stage of T1 for the 15 included nonrandomized studies[28-34,36,37,39-42,45,49] that reported this characteristic ranged from 22.4 percent to 83.5 percent.

Eight studies[28,29,31,39-42,45] also included patients with T3–T4 clinical stage ranging from 0 to 12 percent.

One study[30] reported the mean Gleason scores of 6.8 for RP, 6.0 of CRT, and 5.7 for BT. Five studies did not report Gleason scores.[35-37,42,45] The remaining 13 studies reported the Gleason scores categorically.

Six out of 20 nonrandomized studies did not report preoperative PSA levels for each group of men.[32,35,36,40,45,49] One study reported mean PSA of 7.9, for RP, 10.1 for 3D-CRT, and 6.9 for BT;[30] five reported PSA categorically;[37,39,42-44] and seven reported median PSA levels that ranged from a low of 4.9 to a high of 10.3.[27-29,31,33,34,41]

Four studies had an outcome measure of all-cause mortality,[28,36,38,41] eight studies had an outcome measure of prostate cancer–specific mortality,[31-33,36,38,42,43,49] three studies had an outcome measure of overall survival,[31,43,49] one study reported biochemical failure,[28] three studies reported biochemical progression–free survival,[27-29] one study reported progression to metastasis,[28] one study reported overall quality of life measures,[30] and nine studies reported adverse events, which they sometimes referred to as quality of life measures.[28,30,34,35,37,39,40,44,45] (See Table 17.)

Table 17. Overview of nonrandomized comparative studies (20 studies): Key Question 1

Study	Number of Patients	Subjects	Outcomes	Duration
Resnick et al., 2013[44]	RRP: 1,164 patients	Median age: 64 years; Gleason score 2–4: 63.9%	QOL—urinary function QOL—bowel function QOL—sexual function	15-year followup
	Radiotherapy: 491 patients	Median age 69 years; Gleason score 2–4: 63.9%		
Abdollah et al., 2012[32]	Radiotherapy: 46,521 patients	Age: 65–69 years: 24.1% 70–74 years: 41.4% 75–80 years: 34.5% Gleason score: <6: 5.5% 6–7: 67.8% 8–10: 26.7%	PCSM	10-year followup
	Observation: 22,276 patients	Age: 65–69 years: 21.8% 70–74 years: 34.0% 75–80 years: 44.2% Gleason score: <6: 17.5% 6–7: 67.6% 8–10: 14.8%		
Barry et al., 2012[35]	Robotic-assisted laparoscopic radical prostatectomy: 406 patients	66–69 years: 41.1%; 70–74 years: 43.8%; 75 years or older: 15.0%	Continence Sexual function	14 months postoperation
	ORRP: 220 patients	66–69 years: 38.2%; 70–74 years: 46.4%; ≥75 years: 15.5%		
Kibel et al., 2012[31]	RP: 6,485 patients, 2,843 at site 1 and 3,642 at site 2	Median age at site 1, 2: 60 years and 61 years bGS 2–6 at site 1, 2: 70% and 76%	Overall survival PCSM	10-year followup

Table 17. Overview of nonrandomized comparative studies (20 studies): Key Question 1 (continued)

Study	Number of Patients	Subjects	Outcomes	Duration
	3D-CRT plus IMRT: 2,264 patients, 1,638 at site 1 and 626 at site 2	Median age at site 1, 2: 69 years and 70 years bGS 2–6 at site 1, 2: 47% and 61%		
	BT: 1,680 patients, 1,330 at site 1 and 350 at site 2	Median age site 1, 2: 68 years and 69 years bGS 2–6 at site 1, 2: 81% and 89%		
Mohammed et al., 2012[39]	BT: 417 patients (HDR=210, LDR=207)	Mean age: 64.9 years Gleason score 4–6: 89%	Acute and late genitourinary and gastrointestinal toxicities	Median 4.8 years followup
	EB-IGRT: 1,039 patients	Mean age: 70.8 years Gleason score 4–6: 53%		
	EBRT plus HDR: 447 patients	Mean age: 67.1 years Gleason score 4–6: 36%		
Rosenberg et al., 2012[33]	BT plus EBRT: 186 patients	Median age: 67.8 years Gleason score n (%): ≤6: 24 (12.9%) 3+4: 97 (52.1%) 4+3: 65 (34.9%)	PCSM	4.4 and 4.8 years followup, respectively
	BT plus ADT: 621 patients	Median age: 72.5 years Gleason score n (%): ≤6: 254 (40.9%) 3+4: 252 (40.5%) 4+3: 115 (18.5%)		
Sheets et al., 2012[45]	IMRT: 6,666 patients	Age at diagnosis: 66–69 years: 1,338 (20.1%) 70–74 years: 2,415 (36.2%) 75 years or older: 2,913 (43.7) Tumor grade well/moderately differentiated: 3,390 (50.9%)	Gastrointestinal morbidity Urinary incontinence Nonincontinence urinary morbidity Sexual dysfunction Hip fractures	Median followup for IMRT vs. PBT was 46 and 50 months, respectively. Median followup for the IMRT vs. 3D-CRT was 44 and 64 months, respectively
	3D-CRT: 6,310 patients	Age at diagnosis: 66–69 years: 1,265 (20.1%) 70–74 years: 2,345 (37.2%) 75 years or older: 2,700 (42.8) Tumor grade well/moderately differentiated: 3,850 (61.0%)		

Table 17. Overview of nonrandomized comparative studies (20 studies): Key Question 1 (continued)

Study	Number of Patients	Subjects	Outcomes	Duration
	PBT: 685 patients	Age at diagnosis: 66–69 years: 248 (36.2%) 70–74 years: 233 (34.0%) 75 years or older: 204 (29.8%) Tumor grade well/moderately differentiated: 413 (60.3%)		
Shen et al., 2012[42]	BT: 910 patients	Median age: 70 years T1: 37.4% T2: 59.2% T3: 3.4%	PCSM	Median 6.4 years followup
	BT plus EBRT: 2,466 patients	Median age: 70 years T1: 26.0% T2: 68.6% T3: 5.4%		
	EBRT: 9,369 patients	Median age: 72 years T1: 22.4% T2: 66.8% T3: 10.8%		
Abdollah et al., 2011[49]	RP: 22,244 patients	Mean age: 69.8 years Gleason score 2–5: 4.9% 6–7: 68.2% 8–10: 26.9%	PCSM Other-cause mortality	10-year followup
	Observation: 22,450 patients	Mean age: 73.5 years Gleason score: 2 to 5: 17.6% 6–7: 67.6% 8–10: 14.8%		
Bekelman et al., 2011[40]	IMRT: 5,845 patients	Age at diagnosis: 65–74 years: 55% Gleason score 5–7: 70%	Bowel complications Erectile complications Urinary complications	2-year followup
	3D-CRT: 6,753 patients	Age at diagnosis: 65–74 years: 55% Gleason score 5–7: 68%		
Williams et al., 2011[37]	BT: 9,985 patients	65–69 years: 3,233 (32.4%) 70–74 years: 3,643 (36.5%) ≥75: 3,109 (31.1%) Tumor grade well/moderately differentiated: 84.5%	Urinary complications Bowel complications Erectile dysfunction	Patients had to have 2 years' or more followup to be included
	Cryotherapy: 943 patients	65–69 years: 218 (23.1%) 70–74 years: 366 (35.6%) 75 years or older: 389 (41.3%) Tumor grade well/moderately differentiated: 60.6%		

Table 17. Overview of nonrandomized comparative studies (20 studies): Key Question 1 (continued)

Study	Number of Patients	Subjects	Outcomes	Duration
Barocas et al., 2010[27]	RRP: 491 patients	Mean age: 62 years (7.3) Biopsy Gleason score ≤6: 66.6%	Biochemical recurrence-free survival	3 years of followup
	RALP: 1,413 patients	Mean age: 61 years (7.3) Biopsy Gleason score ≤6: 69.9%		
Malcolm et al., 2009[34]	Open radical prostatectomy: 135 patients	Mean (SD): 59 (7) Gleason score ≤6: 69%	QOL—urinary function QOL—urinary bother QOL—sexual function QOL—sexual bother QOL bowel function QOL bowel bother	3-year followup
	Robotic-assisted prostatectomy: 447 patients	Mean (SD): 59 (6) Gleason score ≤6: 60%		
	BT: 122 patients	Mean (SD): 66 (7) Gleason score ≤6: 72%		
	Cryotherapy: 81 patients	Mean (SD): 71 (7) Gleason score ≤6: 50%		
Hadley et al., 2010[38]	RP: 11,936 patients	Not reported	All-cause and prostate cancer–specific survival and mortality	Up to 12 years
	Conservative management: 5,879 patients	Not reported		
Dosoretz et al., 2010[41]	BT: 1,391 patients	Median age was 73 years for all patients enrolled. For patients younger than 73 years: Gleason score: ≤6: 641(90%) 7: 60 (8%) 8–10: 10 (1%)	All-cause mortality	Median 4.8 years followup
	BT plus ADT: 1,083 patients	Median age of all patients enrolled was 73 years. For patients younger than 73 years: Gleason score: ≤6: 426 (86%) 7: 54 (11%) 8-10: 15 (3%)		
Krambeck et al., 2008[28]	RRP: 588 patients	Median age at surgery: 61 years (range 41 to 77) Biopsy Gleason grade: <6: 0 (0%) 6: 441 (75.0%) 7: 133 (22.6%) ≥8: 14 (2.3%)	Immediate (<1 month postoperative) and late (>1 month postoperative) QOL to determine complications	Median followup was 1.3 years

Table 17. Overview of nonrandomized comparative studies (20 studies): Key Question 1 (continued)

Study	Number of Patients	Subjects	Outcomes	Duration
	Robotic-assisted radical prostatectomy: 294 patients	Median age at surgery: 61 years (38–76) Biopsy Gleason grade: <6: 2 (0.7%) 6: 212 (72.1%) 7: 70 (23.8%) ≥8: 10 (3.4%)	PCSM Other-cause mortality Biochemical progression Systemic progression Clinical local recurrence	
Lu-Yao et al., 2008[36]	Primary ADT: 7,867 patients	Median (IQR) 79 (74–83) Cancer grade: Moderately differentiated: 65.0%	Prostate cancer–specific survival and overall survival	Median followup for overall survival was 81 months
	Conservative management: 11,404 patients	Median IQR 77 (72–81) Moderately differentiated: 83.7%		
Schroeck et al., 2008[29]	RRP: 435 patients	Median age 60.3 years Biopsy Gleason score 2–6: 58.8%	Prostate-specific antigen recurrence rate	Mean followup 1.37 and 1.09 years, respectively
	RALP: 362 patients	Median age 59.2 Biopsy Gleason score 2–6: 72.2%		
Albertsen et al., 2007[43]	Surgery: 596 patients	Median age: 65 years % Gleason score: 2–4: 3% 5: 5% 6: 53% 7: 27% 8–10: 12%	Prostate cancer–specific survival Overall survival	13 year followup
	Radiation: 642 patients	Median age: 71 years % Gleason score: 2–4: 3% 5: 6% 6: 46% 7: 25% 8–10: 20%		
	Observation: 114 patients	Median age: 70 years % Gleason score: 2–4: 17% 5: 15% 6: 46% 7: 11% 8–10: 11%		

Table 17. Overview of nonrandomized comparative studies (20 studies): Key Question 1 (continued)

Study	Number of Patients	Subjects	Outcomes	Duration
Ferrer et al., 2008[30]	RP: 134 patients	Mean age: 64 years (5.5) Mean Gleason score: 6.8 (6.2)	QOL	2 year followup
	3D-CRT: 205 patients	Mean age: 69.2 (5.5) Mean Gleason score: 6.0 (1.1)		
	BT: 275 patients	Mean age: 66.9 years (6.5) Mean Gleason score: 5.7 (4.4)		

3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; bGS=baseline Gleason score; BT=brachytherapy; CI=confidence interval; EB-IGRT=external beam image-guided radiation therapy; EBRT=external beam radiation therapy; HDS=high dose rate; IMRT=intensity-modulated radiation therapy; IQR=interquartile range; LDR=low dose rate; ORRP=open retropubic radical prostatectomy; PBT=proton beam therapy; PCSM=prostate cancer–specific mortality; QOL=quality of life; RALP=robotic-assisted laparoscopic prostatectomy; RP=radical prostatectomy; RR=risk ratio; RRP=radical retropubic prostatectomy.

Risk of Bias

Our risk-of-bias assessments for the 20 nonrandomized comparative studies appear in Table 47 of Appendix D. All 20 nonrandomized comparative studies were categorized as high risk of bias for all of their reported outcomes (see Table 11 for risk of bias assessment criteria).

Findings

All abstracted data for the outcome measures that address this KQ appear in Table 53, Table 55, Table 57, Table 59, Table 61, Table 63, Table 65, and Table 67 of Appendix G.

A. Robotic Radical Prostatectomy Versus Radical Retropubic Prostatectomy (Three Studies)[27-29]

All-Cause Mortality

Krambeck et al.[28] compared RRP to robotic-assisted laparoscopic prostatectomy (RALP) and reported that four patients in each group experienced a death from any cause during the study (4/588 or 0.7 percent, 4/294 or 1.4 percent, respectively). The median followup time was 1.3 years.[28]

Prostate Cancer–Specific Mortality

Krambeck et al.[28] reported no deaths in either treatment group that were attributable to prostate cancer during the study (0/588, 0/294, respectively).

Biochemical Failure

Krambeck et al.[28] reported that 32/588 (5.4 percent) cases of PSA progression were found in the RRP group and 14/294 (4.8 percent) cases of PSA progression were found in the RALP group during the study. There were also 5 cases and 3 cases of clinical local recurrence in the RRP and RALP groups, respectively. The authors report that the groups were similar on margin positivity.

Biochemical Progression-Free Survival

All three trials[27-29] comparing RRP to RALP reported this outcome and none of the three studies found a significant between-group difference. Krambeck et al.[28] reported the mean (SEM) percent of patients that were free of PSA progression (92.2 percent (1.8 percent) and 92.4 percent (2.3 percent) was similar for the RRP and RALP groups, respectively, based on a 3-year Kaplan Meier survival curve analysis. Barocas et al.[27] found no between-group difference in 3-year recurrence-free survival rates between the RRP (83.5 percent) and RALP (84.0 percent), p=0.19.[27] Schroeck et al.[29] used Cox regression analysis, controlling for clinical variables and patient characteristics, at a mean followup of 1.37 years for RRP and 1.09 years for the RALP patients. They reported an HR of 0.82 (95% CI, 0.48 to 1.38), p=0.448. They also performed a similar analysis controlling for risk category and for clinical and pathological variables combined, which found similar results.

Progression to Metastasis

Krambeck et al.[28] reported only one patient in the RALP progressed to metastasis during the study.

Adverse Events

Krambeck et al.[28] reported both early (1 month or less) and late (more than 1 month) postsurgical complications. Wound herniation was more following robotic-assisted radical prostatectomy (RARP; 1.0 percent vs. none, p=0.038), and development of bladder neck contracture was more common after RRP (1.2 percent vs. 4.6 percent, p<0.018). At 1-year followup, there was no significant difference in continence (RARP 91.8 percent, RRP 93.7 percent, p=0.344) or potency (RARP 70.0 percent, RRP 62.8 percent, p=0.081) rates.

B. Radical Prostatectomy Versus Three-Dimensional Conformal Radiation Therapy Versus Brachytherapy (One Study)[30]

Quality of Life

Ferrer et al.[30] reported several measures of health-related quality of life including the short-form (SF)-36, Functional Assessment of Cancer Therapy (FACT), American Urologic Association Symptom Index (AUA-7), and Expanded Prostate Cancer Index Composite (EPIC). The authors found that by the 2-year followup, RP patients had more sexual dysfunction and incontinence than patients treated with either BT or EBRT. Patients receiving EBRT had more bowel and sexual problems than did patients in the BT group. BT was associated with more moderate urinary irritation than RP. No significant between-group differences were found for the SF-36.

C. Radical Prostatectomy Versus External Beam Radiation Therapy (Three-Dimensional Conformal Radiation Therapy or Intensity-Modulated Radiation Therapy) Versus Brachytherapy (One Study)[31]

Overall Survival

In the trial by Kibel et al.[31] EBRT consisted of 3D-CRT and IMRT at various time points during the course of the study. In addition, 34 percent (N=1,348) treated with EBRT and BT received neoadjuvant, concurrent and/or adjuvant ADT. The authors reported that the 10-year

adjusted overall survival after RP, EBRT (3D-CRT and IMRT) and BT was 88.9 percent, 82.6 percent, and 81.7 percent, respectively. Using propensity scoring, EBRT was associated with a reduction in the overall survival (HR 1.6, 95% CI, 1.4 to 1.9, p<0.001) compared with overall survival with RP. BT was also associated with a reduction in overall survival (HR 1.7, 95% CI, 1.4 to 2.1, p<0.001) compared with overall survival in the RP group.

Prostate Cancer–Specific Mortality

Kibel et al.[31] used propensity scoring to report that EBRT and reported that EBRT was associated with an increase in the prostate cancer–specific mortality (HR 1.5; 95% CI, 1.0 to 2.3, p=0.041) compared with RP. Additionally, they reported that BT was also associated with an increase in prostate cancer–specific mortality (HR 1.3, 95% CI, 0.7 to 2.4, p=0.5) compared with that rate in the RP group.

D. Radical Prostatectomy Versus External Beam Radiation Therapy (One Study)[44]

Adverse Events

Resnick et al.[44]compared and reported long-term urinary, bowel, and sexual function after RP or EBRT. At 2 years, patients who underwent RP were more likely to have urinary incontinence (odds ratio [OR], 6.22; 95% CI, 2.29 to 11.36) compared with urinary incontinence in patients who received EBRT. Likewise, patients who underwent RP were more likely to have erectile dysfunction at 2 years (OR, 3.46; 95% CI, 1.93 to 6.17). Finally, patients who underwent RP were less likely to have bowel urgency at 2 years (OR, 0.39; 95% CI, 0.22 to 0.68) and 5 years (OR, 0.47; 95% CI, 0.26 to 0.84). There were, however, no significant between-group difference at 15 years for urinary incontinence, erectile dysfunction, and bowel urgency.

E. Radical Prostatectomy Versus Observation (One Study)[49]

All-Cause Mortality

Abdollah et al.[49] reported that RP was associated with a significant reduction in all-cause mortality (HR 0.57; 95% CI, 0.53 to 0.62; p<0.001) compared with observation.

Prostate Cancer–Specific Mortality

Abdollah et al.[49] reported that RP was associated with a significant reduction in prostate cancer–specific mortality (HR 0.48; 95% CI, 0.38 to 0.59; p<0.001) compared with prostate cancer–specific mortality in the observation group.

F. Brachytherapy Plus External Beam Radiation Therapy Versus Brachytherapy Plus Androgen-Deprivation Therapy (One Study)[33]

Prostate Cancer–Specific Mortality

Rosenberg et al.[33] reported that patients who received BT plus EBRT had an increased risk of prostate cancer–specific mortality (adjusted HR 4.03; 95% CI, 1.17 to 13.89; p=0.027). A Gleason score of 4+3 and elevated PSA were associated with worse prostate cancer–specific mortality (adjusted HR 8.88; 95% CI, 1.10 to 72.04; p=0.04 and adjusted HR 8.03; 95% CI, 2.38 to 28.80; p=0.0014, respectively). At 5 years, estimates of prostate cancer–specific mortality

were 3.3 percent (95% CI, 1.02 to 7.77) in men who received BT plus EBRT compared with 1.1 percent (95% CI, 0.42 to 2.51) in men who received BT plus ADT.

G. Open Radical Prostatectomy Versus Robotic Radical Prostatectomy Versus Cryotherapy Versus Brachytherapy (One Study)[34]

Quality of Life

Malcolm et al.[34] reported Cox proportional HR for returning to 90 percent of the baseline score for urinary function and bother, sexual function and bother, and bowel function and bother. The authors found that BT and cryotherapy patients had better rates of returning to baseline urinary function than both surgery groups. Sexual function was better in the BT group compared with sexual function in the other three treatment groups. Bowel function and bother were not greatly affected by any of the treatments assessed.

H. Robotic Prostatectomy Versus Open Retropubic Prostatectomy (One Study)[35]

Quality of Life

Barry et al.[35] compared the risks of problems with incontinence and sexual function after RALP or RRP. The percentage of patients in each group with moderate to big problems with incontinence and sexual dysfunction was reported. For incontinence 131/393 (33.3 percent) Robotic-assisted laparoscopic radical prostatectomy (RALRP) patients reported moderate to big problems with incontinence versus 58/214 (27.1 percent) patients in the open retropubic radical prostatectomy (ORRP) group. Multivariate analysis controlling for mental health, overall health, age, and education found RALRP to be associated with greater problems with incontinence (OR 1.46; 95% CI, 1.00 to 2.12; p=0.049). For sexual dysfunction 335/383 (87.5 percent) RALRP patients reported moderate to big problems versus 187/210 (89.0 percent) patients in the ORRP group. Multivariate analysis controlling for mental health, overall health, age, and education found no between-group difference in sexual dysfunction (OR 0.93; 95% CI, 0.54 to 1.61; p=0.761).

I. Conservative Management Versus Androgen-Deprivation Therapy (One Study)[36]

All-Cause Mortality

Lu-Yao et al.[36] reported overall mortality rate per 100 was higher in the ADT group (11.9) compared with conservative management (9.5) (adjusted HR 1.17; 95% CI, 1.12 to 1.21; $p<0.05$). The authors conclude that ADT was not associated with improved survival when compared with conservative management. The patients in the conservative management study arm were men who did not receive surgery, radiation, or primary androgen-deprivation therapy during the study duration.

Prostate Cancer–Specific Mortality

Lu-Yao et al.[36] reported the prostate cancer–specific mortality rate per 100 was higher in the ADT group (2.6) compared with that rate in the conservative management group (1.3) (adjusted HR 1.76; 95% CI, 1.59 to 1.95; p<0.05).

J. Brachytherapy Versus Cryotherapy (One Study)[37]

Adverse Events

Williams et al.[37] compared and reported the percentage of patients in each treatment group with urinary, bowel, and erectile complications. Overall, BT patients had significantly more complications than patients receiving cryotherapy (63.6 percent vs. 48.8 percent, respectively, p<0.001). The authors conclude that cryotherapy was associated with more urinary and erectile complications but fewer bowel complications than BT.

K. Brachytherapy Versus Image-Guided External Beam Radiotherapy Versus High Dose–Rate External Beam Radiotherapy (One Study)[39]

Adverse Events

Mohammed et al.[39] compared and reported the percentage of patients in each treatment group with acute and late genitourinary and gastrointestinal events of different severity levels and probability values of the difference. The authors also reported that the incidence of any acute ≥Grade 2 gastrointestinal or genitourinary toxicities were 35% (BT), 49% (EB-IGRT), and 55% (EBRT+HDR), p <0.001. The incidence of urethral stricture and urinary retention was higher among men who received EBRT+HDR, while dysuria was most common among men who received BT alone. The 3-year rates for rectal bleeding was 0.9% (BT), 20% (EB-IGRT), and 6% (EBRT+HDR), p <0.001. Overall, the authors conclude that the three treatments have different toxicity profiles. Patients in the HDR-EBRT group had more urethral strictures and retention whereas BT patients had more dysuria. Rectal bleeding occurred at a higher rate in the image guided EBRT group.

L. Intensity-Modulated Radiation Therapy Versus Three-Dimensional Conformal Radiotherapy (One Study)[40]

Adverse Events

Bekelman et al.[40] compared and reported HRs for between-group differences in bowel, urinary, erectile, proctitis and hemorrhage, and cystitis and hematuria complications. Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis and location of residence were: bowel complications (HR 0.86; 95% CI, 0.79 to 0.93), urinary complications (HR 0.93; 95% CI, 0.83 to 1.04), erectile complications (HR 1.50; 95% CI, 1.00 to 2.24), proctitis, hemorrhage complications (HR 0.78; 95% CI, 0.64 to 0.95) and cystitis, hematuria complications (HR 0.94; 95% CI, 0.83 to 1.07). The authors concluded that IMRT was associated with a small reduction in bowel complications and proctitis and hemorrhage compared with 3D-CRT.

M. Intensity-Modulated Radiation Therapy Versus Proton Beam Therapy Versus Three-Dimensional Conformal Radiotherapy (One Study)[45]

Adverse Events

Sheets et al.[45] reported RRs for gastrointestinal events, urinary events, erectile dysfunction and hip fractures. For the IMRT versus 3D-CRT, the RRs were: gastrointestinal procedures including colonoscopy: RR 1.02, 95% CI, 0.97 to 1.07; urinary incontinence procedures, RR 1.05, 95% CI, 0.98 to 1.12; erectile dysfunction procedures, RR 0.90, 95% CI, 0.75 to 1.09; and for hip fracture, RR 0.78, 95% CI, 0.65 to 0.93.

For IMRT versus proton beam therapy the RR were: gastrointestinal procedures including colonoscopy, RR 0.82, 95% CI, 0.70 to 0.97; urinary incontinence procedures, RR 0.97, 95% CI, 0.77 to 1.20; erectile dysfunction procedures, RR 0.61, 95% CI, 0.35 to 1.06; and for hip fracture RR could not be calculated because of the small number of events. The authors concluded that IMRT was associated with fewer diagnoses of gastrointestinal morbidity and hip fractures, but more erectile dysfunction. Proton beam therapy was associated with more gastrointestinal morbidity than IMRT.

N. Brachytherapy Versus Brachytherapy Plus Androgen-Deprivation Therapy (One Study)[41]

All-Cause Mortality

Dosoretz et al.[41] reported a significant between-group difference in rates of all-cause mortality (HR 0.049; 95%; CI, 0.0006 to 0.403; p=0.0049) in favor of BT plus ADT.

O. Brachytherapy Versus External Beam Radiotherapy Versus Brachytherapy Plus External Beam Radiotherapy (One Study)[42]

Prostate Cancer–Specific Mortality

Shen et al.[42] compared and reported a significant difference in prostate cancer–specific mortality (HR 0.77; 95% CI, 0.66 to 0.90; p<0.01) in favor of BT plus EBRT at a median followup of 6.4 years. The 10-year prostate cancer–specific mortality rate was 21.1 percent for EBRT, 11.3 percent for BT alone, and 13.4 percent for BT plus EBRT.

P. Observation Versus Radiotherapy (One Study)[32]

Prostate Cancer–Specific Mortality

Abdollah et al.[32] compared and reported there was no between-group difference in the clinical effectiveness of observation versus radiotherapy for patients with low to intermediate risk prostate cancer on 10-year prostate cancer–specific mortality (4.1 percent vs. 3.7 percent, respectively, p=0.10). For patients in the high-risk group, 10-year prostate cancer–specific mortality was 14.4 percent in the observation group versus 8.8 percent in the radiotherapy group (p=0.001) in favor of radiotherapy.

Q. Radical Prostatectomy Versus External Beam Radiotherapy Versus Observation (One Study)[43]

Overall Survival

Albertsen et al.[43] reported estimated case fatality rates at 10 years was 4.4 percent for RP, 9.3 percent for EBRT, and 13.5 percent for observation. At an average of 13.3 years followup, RP was associated with improved overall survival compared with overall survival in the other two groups. In this study, patients who underwent RP had less comorbidity and were an average of 5 years younger than patients in the EBRT and observation groups.

Prostate Cancer–Specific Mortality

Albertsen et al.[43] reported that the average prostate cancer rates in patients receiving EBRT were 2.2 times higher (95% CI, 1.6 to 3.1) than that of patients who underwent RP and for the observation group average prostate cancer rates were 3.4 times higher (95% CI, 1.9 to 5.9). In an assessment that was limited to RP or EBRT, the prostate cancer mortality ratio was 2.5 times higher (95% CI, 1.7 to 3.5) in EBRT patients when adjustment was done using covariates directly in the Cox model. At the 15-year followup period, prostate cancer–specific mortality rate was 8 percent in the RP patients and 17 percent in the EBRT patients.

R. Radical Prostatectomy Versus Conservative Management (One Study)[38]

All-Cause Mortality

Hadley et al.[32] compared all-cause mortality data using three analytical approaches. Using the traditional multivariable survival analysis method, they found that conservative management was associated with greater risk of all-cause mortality (HR, 1.47; 95% CI, 1.35 to 1.59) than radical prostatectomy. Using the propensity score adjustment method, they still found that conservative management was associated with greater risk of all-cause mortality than radical prostatectomy. But using the instrumental variable approach, the study did not find a significant difference between the two treatment groups.

Prostate Cancer–Specific Mortality

Using the traditional multivariable survival analysis method, Hadley et al.[32] found that conservative management was associated with greater risk of prostate cancer–specific mortality (HR, 1.59; 95% CI, 1.27 to 2.00) than radical prostatectomy. Using the propensity score adjustment method, they still found that conservative management was associated with greater risk of prostate cancer–specific mortality. Using the instrumental variable approach, the study did not find a significant difference between the two treatment groups.

Summary of Key Question 1

A summary of the comparisons and outcomes we examined for KQ 1 is in Table 15. The overall evidence based on RCTs alone was sufficient to permit a conclusion for four outcomes:

- One outcome favored RP compared with WW (all-cause mortality at the end of the 15-year followup period) based on the SPCG-4 trial[25]

- One outcome favored RP compared with WW (prostate cancer–specific mortality at the end of the 15-year followup period) based on the SPCG-4 trial[25]
- One outcome favored EBRT plus ADT compared with EBRT alone (overall survival) based on both studies being statistically significant in the same direction[24,26]
- One outcome favored EBRT plus ADT compared with EBRT alone (prostate cancer–specific mortality) based on both studies being statistically significant in the same direction[24,26]

Our SOE grades for these patient-oriented outcomes also appear in Table 18 for RCTs across treatment categories and Table 19 from RCTs within treatment categories. Although patients with intermediate- or high-risk prostate cancer disease might benefit from RP, it is not clear that patients with low-risk prostate cancer will benefit. The SPCG-4 trial did not have enough of these patients and the PIVOT found no significant difference between treatment strategies (although the results need longer followup and the study was underpowered). As such, these conclusions might not be clinically relevant for all patients with localized prostate cancer. For example, treating low-risk patients with EBRT plus ADT would be considered substantial overtreatment by most national clinical guidelines. The D'Amico et al. study[24] did not include these patients and the Jones et al. study[26] found no difference in this subgroup. Additionally, the dose of radiation in both of these trials was low, and the length of ADT (only 4 months) in the Jones et al. study[26] might be too short for patients with high-risk disease.

The majority of the studies were at medium risk of bias (see the pertinent section above). We found some inconsistencies for some outcomes based on effect sizes on opposite sides of a null effect. All of these outcomes are directly important to clinicians and patients; imprecision was found for some outcomes that precluded conclusions given the fact that probability values and/or confidence intervals were not reported or could not be calculated.

Table 20 summarizes SOE gradings for the nonrandomized comparative studies that addressed KQ 1.

Table 18. Key Question 1: Strength of evidence grades for randomized controlled trials across primary treatment categories

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. WW[25] (1 study, N=695)	All-cause mortality at the end of the 15-year followup period	Low	Consistency unknown (single study)	Direct	Precise RR 0.75 (95% CI, 0.61 to 0.92) Effect size was statistically significant.	RP	Low
RP vs. WW[25] (1 study, N=695)	PCSM at the end of the 15-year followup period	Low	Consistency unknown (single study)	Direct	Precise RR 0.62 (95% CI, 0.44 to 0.87) Effect size was statistically significant.	RP	Low
RP vs. WW[16,46] (2 studies, N=1,426)	All-cause mortality at the end of the 12-year followup period	Medium	Consistent	Direct	Imprecise SPCG-4 trial: RR 0.94 (95% CI, 0.81 to 1.09) Effect size was not statistically significant. PIVOT: RR 0.88 (95% CI, 0.71 to 1.08) Effect size was not statistically significant.	Inconclusive evidence	Insufficient
RP vs. WW[16,46] (2 studies, N=1,426)	PCSM at the end of the 12-year followup period	Medium	Consistent	Direct	Imprecise SPCG-4 trial: RR 0.65 (95% CI, 0.45 to 0.94) Effect size was statistically significant PIVOT: RR 0.68 (95% CI, 0.40 to 1.17) Effect size was not statistically significant.	Inconclusive evidence	Insufficient
RP vs. WW[47] (1 study, N=695)	Quality of life	Medium	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient
RP vs. BT[21] (1 study, N=200)	Quality of life	Medium	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient

BT=brachytherapy; CI=confidence interval; PCSM=prostate cancer–specific mortality; RP=radical prostatectomy; RR=relative risk; RRP=radical retropubic prostatectomy; SOE=strength of evidence; WW=watchful waiting.

Table 19. Key Question 1: Strength of evidence grades for randomized controlled trials within primary treatment categories

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
EBRT vs. EBRT plus (ADT)[24,26] (2 studies, N=2,185)	Overall survival	Medium	Consistent	Direct	Precise Both studies showed statistically significant between-group differences in the same direction	EBRT plus ADT	Low
EBRT vs. EBRT plus ADT[24] (1 study, N=206)	All-cause mortality	Medium	Consistency unknown (single study)	Direct	Precise Hazard ratio 1.8 (95% CI, 1.1 to 2.9) Effect size was statistically significant	EBRT plus ADT	Low
EBRT vs. EBRT plus ADT[24,26] (2 studies, N=2,185)	PCSM	Medium	Consistent	Direct	Precise Both studies showed statistically significant between-group differences in the same direction	EBRT plus ADT	Low
EBRT vs. EBRT plus ADT[26] (1 study, N=1,979)	Quality of life	Medium	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient
ADT vs. EBRT plus ADT[23] (N=875)	PCSM	Medium	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient

ADT=Androgen-deprivation therapy; CI=confidence interval; EBRT=external beam radiotherapy; PCSM=prostate cancer–specific mortality.

Table 20. Key Question 1: Strength of evidence grades for nonrandomized comparative studies

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. 3D-CRT vs. BT[30] (1 study, N=614)	Quality of life	High	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient
RP vs. EBRT (3D-CRT or IMRT) vs. BT[31] (1 study, N=10,429)	Overall survival at 10-year followup period	High	Consistency unknown (single study)	Direct	EBRT vs. RP: Precise HR 1.6 (95% CI, 1.4 to 1.9) Effect size was statistically significant BT vs. RP: Precise HR 1.7 (95% CI, 1.4 to 2.1) Effect size was statistically significant	Inconclusive evidence	Insufficient
	Prostate cancer-specific mortality at 10-year followup period	High	Consistency unknown (single study)	Direct	EBRT vs. RP: Precise HR 1.5 (95% CI, 1.0 to 2.3) Effect size was statistically significant BT vs. RP: Imprecise HR 1.3 (95% CI, 0.7 to 2.4) Effect size was statistically significant	Inconclusive evidence	Insufficient

Table 20. Key Question 1: Strength of evidence grades for nonrandomized comparative studies (continued)

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
RP vs. observation[49] (1 study, N=49,694)	All-cause-mortality at 10-year followup period	High	Consistency unknown (single study)	Direct	Precise HR 0.57 (95% CI, 0.53 to 0.62). Effect size was statistically significant	Inconclusive evidence	Insufficient
	Prostate cancer-specific mortality at 10-year followup period	High	Consistency unknown (single study)	Direct	Precise HR 0.48 (95% CI, 0.38 to 0.59). Effect size was statistically significant	Inconclusive evidence	Insufficient
BT plus ADT vs. BT plus EBRT[33] (1 study, N=807)	Prostate cancer-specific mortality at 10-year followup period	High	Consistency unknown (single study)	Direct	Precise HR 4.03 (95% CI, 1.17 to 13.89). Effect size was statistically significant	Inconclusive evidence	Insufficient
ORRP vs. RALP vs. Cryotherapy vs. BT[34] (1 study, N=2,000)	Quality of life at 3-year followup	High	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient
Conservative management vs. ADT[36] (1 study, N=19,271)	Overall survival at 10-year followup	High	Consistency unknown (single study)	Direct	Imprecise HR 1.00 (95% CI, 0.96 to 1.05). Effect size was not statistically significant	Inconclusive evidence	Insufficient
	Al-cause mortality rate per 100 at 10-year followup	High	Consistency unknown (single study)	Direct	Precise HR 1.25 (95% CI, 1.21 to 1.30). Effect size was statistically significant	Inconclusive evidence	Insufficient
	Prostate cancer-specific mortality rate per 100 at 10-year followup	High	Consistency unknown (single study)	Direct	Precise HR 2.12 (95% CI, 1.92 to 2.33). Effect size was statistically significant	Inconclusive evidence	Insufficient

Table 20. Key Question 1: Strength of evidence grades for nonrandomized comparative studies (continued)

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
BT vs. BT plus ADT[41] (1 study, N=2,474)	All-cause mortality at median followup of 4.8 years	High	Consistency unknown (single study)	Direct	Precise HR 0.049 (95% CI, 0.0006 to 0.403). Effect size was statistically significant	Inconclusive evidence	Insufficient
BT vs. EBRT vs. BT plus EBRT[42] (1 study, N=12,745)	Prostate cancer-specific mortality at median followup of 6.4 years	High	Consistency unknown (single study)	Direct	Precise HR 0.77 (95% CI, 0.66 to 0.90). Effect size was statistically significant	Inconclusive evidence	Insufficient
RP vs. EBRT[43] (1 study, N=1,618)	Overall survival at 10-year followup	High	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient
	Prostate cancer-specific mortality at 10-year followup	High	Consistency unknown (single study)	Direct	Precise Mortality rate ratio 2.5 times higher (95% CI, 1.7 to 3.5) in the EBRT. Effect size was statistically significant	Inconclusive evidence	Insufficient
RP vs. conservative management[38] (1 study, N=14,302)	Prostate cancer-specific mortality at 10-year followup	High	Consistency unknown (single study)	Direct	Precise HR 1.47 (95% CI, 1.35 to 1.59). Effect size was statistically significant	Inconclusive evidence	Insufficient

3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; bGS=baseline Gleason score; BT=brachytherapy; EBRT=External beam radiotherapy; EB-IGRT=external beam image-guided radiation therapy; EBRT=external beam radiation therapy; HDS=high dose rate; IMRT=intensity-modulated radiation therapy; IQR=interquartile range; LDR=low dose rate; ORRP=open retropubic radical prostatectomy; PBT=proton beam therapy; PCSM=prostate cancer–specific mortality; QOL=quality of life; RALP=robotic-assisted laparoscopic prostatectomy; RP=radical prostatectomy; RRP=radical retropubic prostatectomy.

Key Question 2. How do specific patient characteristics (e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences such as tradeoff of treatment-related adverse effects versus potential for disease progression) affect the outcomes of these therapies overall and differentially?

Randomized Controlled Trials - Comparisons Across Primary Treatment Categories

A. Radical Prostatectomy Versus Watchful Waiting (Two Randomized Controlled Trials)[16,25]

All-Cause Mortality

Wilt et al.[16] found no difference on all-cause mortality when stratified according to age (<65 years: HR 0.89; 95% CI 0.59 to 1.34; ≥65 years: HR 0.84, 95% CI, 0.63 to 1.08), race (White: HR 0.84, 95% CI, 0.65 to 1.08; Black: 0.93, 95% CI, 0.62 to 1.38; Other: HR 0.85, 95% CI, 0.34 to 2.11), Charlson score (0: HR 0.90, 95% CI, 0.66 to 1.21; ≥1: HR 0.84, 95% CI, 0.63 to 1.13), and self-reported performance status between both groups (0: HR 0.89, 95% CI, 0.71 to 1.13; 1-4: HR 0.82, 95% CI, 0.51to 1.31). Bill-Axelson et al.[25] evaluated the interaction between treatment administered and age (younger than 65 years vs. 65 years and older) and reported it was significant for overall mortality (p=0.003), suggesting an advantage of RP among men younger than 65 years of age. Table 21 provides an overview of the RCTs across primary treatment categories that addressed KQ 2. The SOE grades for these studies are reported in Table 24.

Prostate Cancer–Specific Mortality

Wilt et al.[16] reported no difference on prostate cancer–specific mortality when stratified according to age (<65 years: HR 0.52; 95% CI, 0.20 to 1.39; ≥65 years: HR 0.68; 95% CI, 0.34 to 1.33), race (white: HR 0.57, 95% CI, 0.30 to 1.10; Black: 0.80, 95% CI, 0.25 to 2.54; Other: HR 0.56, 95% CI, 0.05 to 6.17), Charlson score (0: HR 0.69, 95% CI, 0.34 to 1.37; ≥1: HR 0.54, 95% CI, 0.21 to 1.38), and self-reported performance status between both groups (0: HR 0.67, 95% CI, 0.37 to 1.23; 1-4: HR 0.41, 95% CI, 0.10 to 1.71). Bill-Axelson et al.[25] evaluated the interaction between treatment administered and age (younger than 65 years vs. 65 years and older) and reported it was insignificant for prostate cancer–specific mortality (p=0.16).

Adverse Events

None of the included RCTs in this category reported adverse events based on patient characteristics.

Table 21. Overview of randomized controlled trials across primary treatment categories (2 trials): Key Question 2

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Wilt et al. 2012[16] Prostate Intervention versus Observation Trial (PIVOT)	Radical prostatectomy: 364 patients vs. observation: 367 patients	Age younger than 75 years, T1/T2, N0, M0, prostate specific antigen (PSA) <50 ng/mL	All-cause mortality Prostate cancer–specific mortality	Median followup 10 years
Bill-Axelson et al. 2011[25] Scandinavian Prostate Cancer Group-4 (SPCG-4) trial	Radical prostatectomy: 347 patients vs. watchful waiting: 348 patients	Age 77 years or younger, T1b, T1c, T2, PSA <50 ng/mL	Overall mortality Prostate cancer–specific mortality	Median followup 15 years

Randomized Controlled Trials – Comparisons Within Primary Treatment Categories

A. External Beam Radiation Therapy Versus External Beam Radiation Therapy Plus Androgen-Deprivation Therapy (Two Randomized Controlled Trials)[24,26]

Overall Survival

Jones et al.[26] separately evaluated white and black patients who were 70 years of age or younger and those who were older than 70 years of age. They reported EBRT plus ADT was advantageous in all these subgroups. When the patients were stratified by race, the 10-year overall survival rate increased from 57 percent to 62 percent among white patients (HR for death with EBRT alone, 1.19; 95% CI, 1.01 to 1.41; p=0.04) and also increased from 55 percent to 61 percent (HR for death with EBRT alone, 1.15; 95% CI, 0.84 to 1.58) among black patients.

Similarly, when the patients were stratified by age, the 10-year overall survival increased from 64 percent to 70 percent among patients who were 70 years of age or younger (HR, 1.23, 95% CI, 0.98 to 1.54) and also increased from 50 percent to 54 percent among men older than 70 years of age (HR, 1.11; 95% CI, 0.92 to 1.33). However, there was no statistical difference between both races (interaction test p=0.79) or between age subgroups (p=0.47).[26] Table 22 provides an overview of the RCTs within primary treatment categories that addressed KQ 2. The SOE grades for these studies are reported in Table 25.

All-Cause Mortality

In the study by D'Amico et al.,[24] there was an increase in all-cause mortality among men who received EBRT with no or minimal comorbidity (31 vs. 11 deaths; HR, 4.2; 95% CI, 2.1 to 8.5; p ,0.001). Among men with moderate or severe comorbidity, those in the EBRT alone group compared to the EBRT +ADT group did not have an increased risk of all-cause mortality (13 vs. 19 deaths; HR, 0.54; 95% CI, 0.27 to 1.10; p=0.08)

Prostate Cancer–Specific Mortality

Jones et al.[26] reported the addition of short-term ADT to EBRT resulted in reduction in the 10-year prostate cancer–specific mortality among black patients from 7 percent to 5 percent (HR with EBRT alone, 1.27; 95% CI, 0.59 to 2.73). Among white patients, EBRT plus ADT was associated with a significantly lower prostate cancer–specific mortality (HR with EBRT alone, 2.33; 95% CI, 1.46 to 3.72; p<0.001). When stratified by age, EBRT plus ADT was associated with a significantly lower cancer-specific mortality in comparison with EBRT alone among men older than 70 years of age (HR 2.19; 95% CI, 1.31 to 3.64; p<0.004). However, for men 70 years of age or younger, prostate cancer–specific mortality was not significantly different between the two treatments (HR 1.43; 95% CI, 0.79 to 2.57).

Biochemical Failure

Jones et al.[26] reported that adding short-term ADT to EBRT resulted in significant reduction in the 10-year biochemical failure among black patients (HR, 2.27; 95% CI, 1.53 to 3.38; p<0.001) and white patients (HR, 1.62; 95% CI, 1.35 to 1.93; p<0.001). Similarly, when stratifying by age, EBRT plus ADT resulted in a significant reduction in the 10-year biochemical failure for men age 70 years or younger (HR, 1.78; 95% CI, 1.41 to 2.23; p<0.001) and men older than 70 years (HR, 1.71; 95% CI, 1.37 to 2.13; p<0.001).

Adverse Events

None of the included RCTs in this category reported adverse events based on patient characteristics.

Table 22. Overview of randomized controlled trials within primary treatment categories (2 trials): Key Question 2

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Jones et al., 2011[26]	EBRT: 992 patients vs. EBRT plus short-term ADT: 987 patients	Age 71 years or younger, T1b, T1c, T2a, T2b, prostate specific antigen ≤20 ng/mL	All-cause mortality Prostate cancer–specific mortality Biochemical failure	Median followup 9.1 years
D'Amico et al. 2008[24]	EBRT: 104 patients vs. EBRT plus ADT: 102 patients	T1, T2 patients who had at least a 10-year life expectancy excluding death from prostate cancer	Overall survival All-cause mortality	Median followup 7.6 years

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy.

Nonrandomized Comparative Studies

A. Brachytherapy Versus Brachytherapy Plus Androgen-Deprivation Therapy (One Study)[41,55]

All-Cause Mortality

Dosoretz et al.[41] reported that in the subgroup of men younger than 73 years of age, BT plus ADT was not associated significantly with an increased risk of all-cause mortality (p=0.34). However, BT plus ADT was associated significantly with an increased risk of all-cause mortality in men aged 73 years or older (adjusted HR 1.24; 95%, CI, 1.01 to 1.53; p=0.037) as age was

increasing (adjusted HR 1.06; 95% CI, 1.03 to 1.09; p=0.002). Table 23 provides an overview of the nonrandomized comparative studies that addressed KQ 2. The SOE grades for these studies are reported in Table 26.

B. Observation Versus Androgen-Deprivation Therapy (One Study)[55]

Prostate Cancer–Specific Mortality

Abdollah et al.[32] reported that in the subgroup of men with a Charlson comorbidity index (CCI) of 0, 1, and ≥2, the 10-year prostate cancer-specific mortality rates were 5.7 percent versus 6.5 percent (HR 0.81; 95% CI, 0.67 to 0.98; p=0.001), 4.6 percent versus 6.0 percent (HR 0.87; 95% CI, 0.75 to 0.99; p=0.01), and 4.2 percent versus 5.0 percent (HR 0.79; 95% CI, 0.65 to 0.96; p=0.01) among patients who underwent EBRT versus observation, respectively. Likewise, the following 10-year prostate cancer–specific mortality rates were reported among patients who underwent EBRT compared with observation, respectively:[32]

- In the subgroup of men aged 65–69 years, 4.1 percent versus 4.5 percent (p=0.7)
- In the subgroup of men aged 70–74 years, 4.8 percent versus 5.1 percent (p=0.6)
- In the subgroup of men aged 75–80 years, 5.6 percent versus. 7.3 percent (HR 0.70; 95% CI, 0.59 to 0.80; p<0.001)

The authors reported that patients in the EBRT group were younger and had lower CCI relative to patients in the observation group.

Table 23. Overview of *nonrandomized comparative studies (2 studies): Key Question 2

Study	Number of Patients	Subjects	Outcomes	Duration
Abdollah et al., 2012[32]	Radiotherapy: 46,521 patients	Age: 65–69 years: 24.1% 70–74 years: 41.4% 75–80 years: 34.5% Gleason score: <6: 5.5% 6–7: 67.8% 8–10: 26.7%	Prostate cancer–specific mortality	10-year followup
	Observation: 22,276 patients	Age: 65–69 years: 21.8% 70–74 years: 34.0% 75–80 years: 44.2% Gleason score: <6: 17.5% 6–7: 67.6% 8–10: 14.8%		

Table 23. Overview of *nonrandomized comparative studies (2 studies): Key Question 2 (continued)

Study	Number of Patients	Subjects	Outcomes	Duration
Dosoretz et al. 2010[41]	BT: 1,391 patients	Median age was 73 years for all patients enrolled. For patients younger than 73 years: Gleason score: ≤6: 641(90%) 7: 60 (8%) 8–10: 10 (1%)	All-cause mortality	Median followup 4.8 years
	BT plus androgen-deprivation therapy: 1,083 patients	Median age of all patients enrolled was 73 years. For patients younger than 73 years: Gleason score: ≤6: 426 (86%) 7: 54 (11%) 8–10: 15 (3%		

BT=Brachytherapy.

*None of the included nonrandomized comparative studies for this key question reported adverse events based on patient characteristics.

Table 24. Key Question 2: Strength of evidence grades for randomized controlled trials across primary treatment categories

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
Radical Prostatectomy (RP vs. watchful waiting (WW)[16]	All-cause mortality for patients (age <65 years [N=93] or ≥65 years [N=261]; white [N=236], black [N=99], other [N=19]; Charlson score 0 [N=168] or ≥1 [N=186]; Performance score 0 [N=285] or 1-4 [N=69]) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient for all patient subgroups
	Prostate cancer-specific mortality for patients (age < 65 years [N=18] or ≥65 years [N=34]; white [N=37], black [N=12], other [N=3]; Charlson score 0 [N=33] or ≥1 [N=19]; Performance score 0 [N=43] or 1-4 [N=9]) at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient for all patient subgroups
RP vs. WW[25]	Overall mortality for patients <age 65 years at 15-year followup (study did not report number of patients in this subgroup)	Low	Consistency unknown (single study)	Direct	Precise Relative risk (RR) (95% confidence interval [CI] 0.52, [0.37 to 0.73]). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup*
	Prostate cancer–specific mortality for patients <age 65 years at 15-year followup (study did not report number of patients in this subgroup)	Low	Consistency unknown (single study)	Direct	Precise RR 0.49 (95% CI, 0.31 to 0.79). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup*

*SOE grading reduced by one level based on subgroup analysis (see methods section for further details).

Table 25. Key Question 2: Strength of evidence grades for randomized controlled trials within primary treatment categories

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
External Beam Radiotherapy (EBRT) vs. EBRT plus short-term androgen deprivation therapy (ADT)[26]	Overall survival among white patients [N=1,505] at 10-year followup.	Medium	Consistency unknown (single study)	Direct	Precise Hazard ratio [HR] 1.19 (95% confidence interval [CI], 1.01 to 1.41). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
	Prostate cancer-specific mortality among white [N=1,505] patients at 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 2.33 (95% CI, 1.46 to 3.72). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
	Prostate cancer-specific mortality among patients age >70 years at [N=1,005] 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 2.19 (95% CI, 1.31 to 3.64). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
EBRT vs. EBRT plus ADT[24]	All-cause mortality among patients with no or minimal comorbidity [N=157] at a median followup of 7.6 years	Low	Consistency unknown (single study)	Direct	Precise HR 4.2 (95% CI, 2.1 to 8.5). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup*
	All-cause mortality among patients with moderate or severe comorbidity [N=49] at a median followup of 7.6 years	Low	Consistency unknown (single study)	Direct	Imprecise HR 0.54 (95% CI, 0.27 to 1.10). Effect size was not statistically significant.	Inconclusive evidence	Insufficient for patient subgroup

*SOE grading reduced by one level based on subgroup analysis (see methods section for further details).

Table 26. Key Question 2: Strength of evidence grades for nonrandomized comparative studies

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
Brachytherapy (BT) vs. BT plus androgen deprivation therapy (ADT)[41]	All-cause mortality among patients age >73 years at a median followup of 4.8 years (study did not report number of patients in this subgroup)	High	Consistency unknown (single study)	Direct	Precise Hazard ratio [HR] 1.24 (95% confidence interval [CI], 1.01 to 1.53). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
Observation vs. ADT[32]	Prostate cancer-specific mortality among men with a Charlson comorbidity score of 0 [N=17,760], 1 [N=11,545], and ≥2 [N=12,667] at 10-year followup	High	Consistency unknown (single study)	Direct	Precise 0 comorbidity: HR 0.81 (95% CI 0.67 to 0.98) 1 comorbidity: HR 0.87 (95% CI 0.75 to 0.99) ≥2 comorbidities: HR 0.79 (95% CI 0.65 to 0.96). Effect size was statistically significant in same direction for each subgroup	Inconclusive evidence	Insufficient for all patient subgroups
	Prostate cancer-specific mortality among men ages 75-80 [N=17,364] at 10-year followup	High	Consistency unknown (single study)	Direct	Precise HR 0.7 (95% CI, 0.59 to 0.80). Effect size was statistically significant	Inconclusive evidence	Insufficient for patient subgroup
	Prostate cancer-specific mortality among men ages 65-69 [N=9,580] and 70-74 [N=15,028] at 10-year followup	High	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient for patient subgroup

Key Question 3. How do provider/hospital characteristics affect outcomes of these therapies overall and differentially (e.g., geographic region, case volume, learning curve)?

We identified eight reports[56-63] that were reviewed by a clinical expert. No comparative studies (RCTS or non-RCTs) were found that examined how provider characteristics influence the effectiveness of different treatments. All eight reports were observational cohort studies. Six reports[56-61] examined the learning curve for clinicians treating patients with radical prostatectomy.

Of the six reports, five[57-61] reported on positive associations between surgeon case volume and biochemical recurrence-free survival. None of these five studies evaluated associations between surgeon case volume and disease-specific or overall survival. One[56] reported on a prospective, single institution evaluation of five residents-in-training. Two reports[62,63] examined the association between provider characteristics and treatment patterns. Both studies used SEER-Medicare data. One study[63] found that patient, provider, and geographic factors are associated with the adoption of minimally invasive radical prostatectomy. One study[62] evaluated the association between visits to surgical, radiation, and medical oncology specialists and treatment, and found that specialist visits relate strongly to prostate cancer treatment choices.

Key Question 4. How do tumor characteristics (e.g., Gleason score, tumor volume, screen-detected versus clinically detected tumors, and PSA levels) affect the outcomes of these therapies overall and differentially?

Randomized Controlled Trials – Comparisons Across Primary Treatment Categories

A. Radical Prostatectomy Versus Watchful Waiting (Two Randomized Controlled Trials)[16,25]

All-Cause Mortality

Wilt et al.[16] reported that RP did not reduce all-cause mortality among men with PSA 10 ng/mL or less (HR 1.03; 95% CI, 0.79 to 1.35). However, among men with PSA of more than 10 ng/mL, RP resulted in a 13.2 percent reduction of all-cause mortality (HR, 0.67; 95% CI, 0.48 to 0.94), indicating that RP might reduce all-cause mortality among men with higher PSA levels. Subgroup analyses of men with intermediate-risk tumor (PSA 10.1–20.0 ng/mL, Gleason score 7, or tumor stage T2b) showed a 31 percent reduction in all-cause mortality following RP compared to observation (HR, 0.69; 95% CI, 0.49 to 0.98). In the high-risk group, RP compared with observation resulted in mortality of 6.7 percent vs. 5.4 percent (HR 0.74, 95% CI, 0.49 to 1.13). The absolute difference at 12 years was 5.4 percentage points in favor of observation compared with RP (37.2 percent versus 31.8 percent, p=0.16).

Bill-Axelson et al.[25] reported PSA level (less than 10 ng/mL vs. 10 ng/mL or more) and Gleason score (less than 7 vs. 7 or more) did not change the beneficial effect of RP (P=0.72 and P=0.36, respectively, for interaction with overall mortality). More specifically, among men with low-risk prostate cancer, an absolute between-group difference of 13.2 percent regarding all-cause mortality at 15-year followup corresponded to RR 0.62 (95% CI, 0.42 to 0.92; p=0.002) and number needed to treat of 8, suggesting a benefit of RP among men in this risk category. This differed from the findings of Wilt et al. However, both studies were consistent in finding reduced mortality associated with RP among patients with PSA >10 ng/mL. Table 27 provides an overview of the RCTs across primary treatment categories that addressed KQ 4. The SOE grades for these studies are reported in Table 30.

Prostate Cancer–Specific Mortality

The Wilt et al. study,[16] which was conducted during the early period of PSA testing, reported that men with a PSA >10 ng/mL in the RP group had lower prostate cancer–specific mortality than did men in observation group (5.6 percent vs. 12.5 percent, p=0.02). Among the high-risk group, the prostate cancer–specific mortality was 9.1 percent in the RP group and 17.5 percent in the observation group, p=0.04.

Bill-Axelson et al.[25] reported that PSA level (less than 10 ng/mL vs. 10 ng/mL or more) and Gleason score (less than 7 vs. 7 or more) did not change the outcome for RP (p=0.30 and p=0.52, respectively, for interaction with prostate cancer–specific mortality). Among men with low-risk prostate cancer who underwent RP compared to observation, an absolute between-group difference of 4.2 percent regarding prostate cancer–specific mortality corresponded to RR 0.53 (95% CI, 0.24 to 1.14; p=0.14).

Distant Metastases

Among men with low-risk prostate cancer who underwent RP compared to WW, Bill-Axelson et al.[25] reported, an absolute between-group difference of 11.4 percent (95% CI, 2.6 to 20.2) regarding distant metastases corresponded to RR 0.43 (95% CI, 0.23 to 0.79; p=0.008).

Adverse Events

None of the included RCTs in this category reported adverse events based on tumor characteristics.

Table 27. Overview of randomized controlled trials across primary treatment categories (2 trials): Key Question 4

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Wilt et al. 2012[16] Prostate Intervention versus Observation Trial (PIVOT)	Radical prostatectomy: 364 patients vs. observation: 367 patients	Age younger than 75 years, T1/T2, N0, M0, prostate specific antigen (PSA) <50 ng/mL	All-cause mortality	Median followup 10 years
Bill-Axelson et al. 2011[25] Scandinavian Prostate Cancer Group-4 (SPCG-4) trial	Radical prostatectomy: 347 patients vs. watchful waiting: 348 patients	Age 77 years or younger, T1b, T1c, T2, PSA <50 ng/mL	Overall mortality Prostate cancer–specific mortality Distant metastases	Median followup 15 years

Randomized Controlled Trials – Comparisons Within Primary Treatment Categories

A. External Beam Radiation Therapy Versus External Beam Radiation Therapy Plus Androgen-Deprivation Therapy (One Randomized Controlled Trial)[26]

Overall Survival

Jones et al.[26] reported that among men in the intermediate-risk subgroup, the 10-year overall survival rate was 54 percent in the EBRT-alone group compared with 60 percent in the EBRT plus short-term ADT group (HR for death with EBRT alone, 1.25; 95% CI, 1.02 to 1.49). Among men in the low-risk subgroup, there was no benefit as shown by a 64 percent rate in the EBRT-alone group compared with 67 percent in the EBRT plus short-term ADT group (HR from death with EBRT alone, 1.07; 95% CI, 0.83 to 1.39). Table 28 provides an overview of the RCTs within primary treatment categories that addressed KQ 4. The SOE grades for these studies are reported in Table 31.

Prostate Cancer–Specific Mortality

Jones et al.[26] reported that among men in the intermediate-risk subgroup, the 10-year prostate cancer–specific mortality was 10 percent in the EBRT-alone group, compared with 3 percent in the EBRT plus short-term ADT group (HR, 2.49; 95% 1.50 to 4.11). No benefit was found in the low-risk subgroup as shown by a 1 percent rate in the EBRT-alone group, compared with 3 percent in the EBRT plus short-term ADT group (HR, 0.63; 95% CI, 0.21 to 1.92).

Biochemical Failure

Jones et al.[26] reported there was a significant reduction in the 10-year biochemical failure in all three risk subgroups (i.e. low-risk [HR, 1.53; 95% CI, 1.13 to 2.06; p<0.001], intermediate-risk [HR, 1.79;95% CI, 1.45 to 2.21; p<0.001], and high-risk [HR, 1.98; 95% CI, 1.30 to 3.03; p=0.002]) among men in the EBRT plus short-term ADT group compared with EBRT-alone group.[26]

Adverse Events

None of the included RCTs in this category reported adverse events for this key question based on patient characteristics.

Table 28. Overview of randomized controlled trials within primary treatment categories (1 trial): Key Question 4

Study	Interventions and Number of Patients	Subjects	Outcomes	Duration
Jones et al. 2011[26]	EBRT: 992 patients vs. EBRT plus short-term androgen-deprivation therapy: 987 patients	Age 71 years or younger, T1b, T1c, T2a, T2b, prostate specific antigen (PSA) ≤20 ng/mL	Overall survival Prostate cancer-specific mortality Biochemical failure	Median followup 9.1 years

EBRT=External beam radiation therapy.

Nonrandomized Comparative Studies

A. Brachytherapy Versus Brachytherapy Plus Androgen-Deprivation Therapy (One Study)[31,32,36,41,64]

All-Cause Mortality

Dosoretz et al.[41] reported that PSA level, biopsy Gleason score, and clinical T classification were not associated with an increased risk of all-cause mortality in both study groups. Table 29 provides an overview of the nonrandomized comparative studies that addressed KQ 4. The SOE grades for these studies are reported in Table 32.

B. Brachytherapy Plus External Beam Radiation Therapy Versus Brachytherapy Plus Androgen-Deprivation Therapy (One Study)[33]

Prostate Cancer–Specific Mortality

Rosenberg et al.[33] reported that a Gleason score of 4+3 (adjusted HR 8.88; 95% CI, 1.10 to 72.04; p=0.04) and an elevated PSA (adjusted HR 8.03; 95% CI, 2.38 to 28.80; p=0.0014), were associated with worse prostate cancer–specific mortality among men who received BT plus

EBRT compared to EBRT plus ADT. Study authors reported that men in the BT plus EBRT group were younger and more likely to have higher Gleason scores of T-categories compared with men who received BT plus ADT.

C. Radical Prostatectomy Versus External Beam Radiation Therapy (Three-Dimensional Conformal Radiation Therapy or Intensity-Modulated Radiation Therapy) Versus Brachytherapy (One Study)[31]

Overall Survival

In the trial by Kibel et al.[31] EBRT consisted of 3D-CRT and IMRT at various time points during the course of the study. The reported data were stratified by tumor risk (low, intermediate, and high). Study authors reported that RP was associated with improved overall survival in all prostate cancer risk categories:

Low risk:	EBRT versus RP (HR 1.7, 95% CI, 1.3 to 2.1, p<0.001) BT versus RP (HR 1.7, 95% CI, 1.4 to 2.2, p <0.001)
Intermediate risk:	EBRT versus RP (HR 1.5, 95% CI, 1.2 to 1.9, p=0.001) BT versus RP (HR 1.5, 95% CI, 1.1 to 2.1, p=0.001)
High risk:	EBRT versus RP (HR 1.7, 95% CI, 1.3 to 2.3, p=0.001) BT versus RP (HR 3.1, 95% CI, 1.7 to 5.9, p <0.001)

Prostate Cancer–Specific Mortality

Kibel et al.[31] reported that there were no significant differences in prostate cancer-specific mortality within each prostate cancer risk category:

Low risk:	EBRT versus RP (HR 1.8, 95% CI, 0.5 to 6.2, p=0.4) BT versus RP (HR 2.3, 95% CI, 0.8 to 6.9, p=0.14)
Intermediate risk:	EBRT versus RP (HR 1.8, 95% CI, 0.8 to 3.8, p=0.13) BT versus RP (HR 0.6, 95% CI, 0.1 to 2.7, p=0.5)
High risk:	EBRT versus RP (HR 1.3, 95% CI, 0.8 to 2.1, p=0.2) BT versus RP (HR 1.6, 95% CI, 0.4 to 6.6, p=0.5)

D. Conservative Management Versus Androgen-Deprivation Therapy (One Study)[36]

All-Cause Mortality

Lu-Yao et al.[36] stratified the reported data by patients' cancer grade (i.e., well-, moderately-, poorly-differentiated). Among men with poorly-differentiated cancer, all-cause mortality rate per 100 was slightly higher in the ADT group (15.3 percent) compared with that rate in the conservative management group (14.4 percent) (adjusted HR 1.04; 95% CI, 0.97 to 1.13) compared with conservative management, but the difference was not statistically significant. Among men with moderately-differentiated cancer, all-cause mortality rate per 100 was significantly higher in the ADT group (10.4 percent) compared with that rate in the conservative management group (8.8 percent) (adjusted HR 1.15; 95% CI, 1.10 to 1.21). Authors did not provide results for men in the well-differentiated prostate cancer subgroup.

Prostate Cancer–Specific Mortality

Lu-Yao et al.[36] reported that among men with poorly-differentiated cancer, prostate cancer-specific mortality rate per 100 was slightly higher in the ADT group (4.7 percent) compared with that rate in the conservative management group (4.1 percent) (adjusted HR 1.12; 95% CI, 0.96 to 1.29) compared with conservative management, but the difference was not statistically significant. Among men with moderately-differentiated cancer, prostate cancer-specific mortality rate per 100 was significantly higher in the ADT group (1.7 percent) compared with that rate in the conservative management group (0.8 percent) (adjusted HR 1.83; 95% CI, 1.58 to 2.12) compared with conservative management. Authors did not provide results for men in the well-differentiated prostate cancer subgroup.

E. Observation Versus External beam Radiotherapy (One Study)[32]

Prostate Cancer–Specific Mortality

Abdollah et al.[32] found no between-group difference in the clinical effectiveness of EBRT versus observation on 10-year prostate cancer–specific mortality for patients with low to intermediate risk prostate cancer (3.7 percent vs. 4.1 percent, respectively, HR 0.91; 95% CI 0.80 to 1.04; p=0.10). For patients in the high-risk group, 10-year prostate cancer–specific mortality was 8.8 percent in the radiotherapy group versus 14.4 percent in the observation group (HR 0.59; 95% CI, 0.50 to 0.68; p=0.001) in favor of radiotherapy.

Table 29. Overview of *nonrandomized comparative studies (5 studies): Key Question 4

Study	Number of Patients	Subjects	Outcomes	Duration
Rosenberg et al. 2012[33]	BT pus external beam radiatiotherapy: 186 patients	Median age: 67.8 years Gleason score n (%): ≤6: 24 (12.9%) 3+4: 97 (52.1%) 4+3: 65 (34.9%)	Prostate cancer–specific mortality	4.4 and 4.8 years followup, respectively
	BT plus ADT: 621 patients	Median age: 72.5 years Gleason score n (%): ≤6: 254 (40.9%) 3+4: 252 (40.5%) 4+3: 115 (18.5%)		
Kibel et al. 2012[31]	RP: 6,485 patients, 2,843 at site 1 and 3,642 at site 2	Median age at site 1, 2: 60 years and 61 years bGS 2–6 at site 1 and 2: 70% and 76%	Overall survival, Prostate cancer–specific mortality	10-year followup
	Three-dimensional conformal radiotherapy plus intensity modulated radiotherapy: 2,264 patients, 1,638 at site 1 and 626 at site 2	Median age at site 1 and 2: 69 years and 70 years bGS 2–6 at site 1 and 2: 47% and 61%		
	BT: 1,680 patients, 1,330 at site 1 and 350 at site 2	Median age site 1, 2: 68 years and 69 years bGS 2–6 at site 1, 2: 81% and 89%		

Table 29 Overview of *nonrandomized comparative studies (5 studies): Key Question 4 (continued)

Study	Number of Patients	Subjects	Outcomes	Duration
Abdollah et al. 2012[32]	Radiotherapy: 46,521 patients	Age: 65–69 years: 24.1% 70–74 years: 41.4% 75–80 years: 34.5% Gleason score: <6: 5.5% 6–7: 67.8% 8–10: 26.7%	Prostate cancer–specific mortality	10-year followup
	Observation: 22,276 patients	Age: 65–69 years: 21.8% 70–74 years: 34.0% 75–80 years: 44.2% Gleason score: <6: 17.5% 6–7: 67.6% 8–10: 14.8%		
Dosoretz et al. 2010[41]	Brachytherapy: 1,391 patients	Median age was 73 years for all patients enrolled. For patients younger than 73 years: Gleason score: ≤6: 641(90%) 7: 60 (8%) 8–10: 10 (1%)	All-cause mortality	Median followup 4.8 years
	Brachytherapy plus androgen-deprivation therapy: 1,083 patients	Median age of all patients enrolled was 73 years. For patients younger than 73 years: Gleason score: ≤6: 426 (86%) 7: 54 (11%) 8–10: 15 (3%)		
Lu-Yao et al. 2008[36]	Primary ADT: 7,867 patients	Median (IQR) 79 (74–83) Cancer grade: Moderately differentiated: 65.0%	Prostate cancer–specific survival and overall survival	Median followup for overall survival was 81 months
	Conservative management: 11,404 patients	Median IQR 77 (72–81) Moderately differentiated: 83.7%		

ADT=Androgen-deprivation therapy; bGS=baseline Gleason score; BT=brachytherapy; RP=radical prostatectomy (RP).
*None of the included nonrandomized comparative studies for this key question reported adverse events based on tumor characteristics.

Table 30. Key Question 4: Strength of evidence grades for randomized controlled trials across primary treatment categories

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
Radical Prostatectomy (RP vs. watchful waiting (WW)[16]	All-cause mortality among patients with prostate specific antigen (PSA) >10 [N=138] at 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise Hazard ratio (HR) 0.67 (95% confidence interval [CI], 0.48 to 0.94). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
	All-cause mortality among patients with PSA ≤10 [N=211]; low- [N=116], intermediate- [N=129], high-risk [N=91] prostate cancer; Gleason score <7 [N=238] or ≥7 [N= 97] at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise Effect size was not statistically significant for all subgroups	Inconclusive evidence	Insufficient for all patient subgroups
	Prostate cancer–specific mortality among patients with PSA ≤10 [N=29] or >10 [N=23]; low- [N=10], intermediate- [N=19], high-risk [N=21] prostate cancer; Gleason score <7 or ≥7 at 10-year followup	Medium	Consistency unknown (single study)	Direct	Imprecise Effect size was not statistically significant for all subgroups.	Inconclusive evidence	Insufficient for all patient subgroups
RP vs. WW[25]	Overall mortality among patients with low-risk prostate cancer at 15-year followup (study did not report number of patients in this subgroup)	Low	Consistency unknown (single study)	Direct	Precise Relative risk (RR) (95% CI 0.62, 0.42 to 0.92). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup*
	Prostate cancer–specific mortality among patients with low-risk prostate cancer at 15-year followup (study did not report number of patients in this subgroup)	Low	Consistency unknown (single study)	Direct	Imprecise RR 0.53 (95% CI, 0.24 to 1.14). Effect size was not statistically significant.	Inconclusive evidence	Insufficient for patient subgroup

*SOE grading reduced by one level based on subgroup analysis (see methods section for further details).

Table 31. Key Question 4: Strength of evidence grades for randomized controlled trials within primary treatment categories

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
External Beam Radiotherapy (EBRT) vs. EBRT plus short-term androgen deprivation therapy (ADT)[26]	Overall survival among patients with intermediate risk [N=1,068] prostate cancer at median followup of 9.1 years	Medium	Consistency unknown (single study)	Direct	Precise Hazard ratio [HR] 1.23 (95% confidence interval [CI], 1.02 to 1.49). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
	Prostate cancer-specific mortality among patients with intermediate risk [N=1,068] prostate cancer at 10-year followup	Medium	Consistency unknown (single study)	Direct	Precise HR 2.49 (95% CI, 1.50 to 4.11). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup

Table 32. Key Question 4: Strength of evidence grades for nonrandomized comparative studies

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
Brachytherapy (BT) vs. BT plus androgen deprivation therapy (ADT)[41]	All-cause mortality among patients stratified by prostate specific antigen (PSA) level, biopsy Gleason score, and clinical T classification at a median followup of 4.8 years (see appendix for reported number of patients in this subgroup based on age <73 years or >73 years)	High	Consistency unknown (single study)	Direct	Imprecise (p-value not reported)	Inconclusive evidence	Insufficient for all patient subgroups

Table32. Key Question 4: Strength of evidence grades for nonrandomized comparative studies (continued)

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
BT plus External Beam Radiotherapy (EBRT) vs. BT plus androgen deprivation therapy (ADT)[33]	Prostate cancer-specific mortality among patients with a Gleason score 4+3 [N=180] at median followup of 4.4 years and 4.8 years, respectively	High	Consistency unknown (single study)	Direct	Precise Hazard ratio [HR] 8.88 (95% confidence interval [CI], 1.10 to 72.04). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
	Prostate cancer-specific mortality among patients with an elevated PSA [N=410] at median followup of 4.4 years and 4.8 years, respectively	High	Consistency unknown (single study)	Direct	Precise HR 8.03 (95% CI, 2.38 to 28.80). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
Radical Prostatectomy (RP) vs. EBRT vs. BT[31]	Overall survival among patients with low risk [N=685] prostate cancer at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Precise HR 1.7 (95% CI, 1.3 to 2.1). Effect size was statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
					RP vs. BT Precise HR 1.7 (95% CI, 1.4 to 2.2). Effect size was statistically significant		

Table32. Key Question 4: Strength of evidence grades for nonrandomized comparative studies (continued)

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
Radical Prostatectomy (RP) vs. EBRT vs. BT[31] (continued)	Overall survival among patients with intermediate risk [N=1,068] prostate cancer at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Precise HR 1.5 (95% CI, 1.2 to 1.9). Effect size was statistically significant		
					RP vs. BT Precise HR 1.5 (95% CI, 1.1to 2.1). Effect size was statistically significant		
	Overall survival among patients with high-risk [N=226] prostate cancer at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs EBRT Precise HR 1.7 (95% CI, 1.3 to 2.3). Effect size was statistically significant		
					RP vs. BT Precise HR 3.1 (95% CI, 1.7 to 5.9). Effect size was statistically significant		

Table32. Key Question 4: Strength of evidence grades for nonrandomized comparative studies (continued)

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
RP vs. EBRT vs. BT[31]	Prostate cancer-specific mortality among patients with low risk [N=685] prostate cancer at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Imprecise HR 1.8 (95% CI, 0.5 to 6.2). Effect size was not statistically significant.	Inconclusive evidence	Insufficient for patient subgroup
					RP vs. BT Imprecise HR 2.3 (95% CI, 0.8 to 6.9). Effect size was not statistically significant		
	Prostate cancer-specific mortality among patients with intermediate risk [N=1,068] prostate cancer at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Imprecise HR 1.8 (95% CI, 0.8 to 3.8). Effect size was not statistically significant		
					RP vs. BT Imprecise HR 0.6 (95% CI, 0.1 to 2.7). Effect size was not statistically significant		
	Prostate cancer-specific mortality among patients with high risk [N=226] prostate cancer at 10-year followup	High	Consistency unknown (single study)	Direct	RP vs. EBRT Imprecise HR 1.3 (95% CI, 0.8 to 2.1). Effect size was not statistically significant.		
					RP vs. BT Imprecise HR 1.6 (95% CI, 0.4 to 6.6). Effect size was not statistically significant.		

Table32. Key Question 4: Strength of evidence grades for nonrandomized comparative studies (continued)

Comparison	Outcome	Overall Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grading
Observation vs. ADT[32]	Prostate cancer-specific mortality among men with low to intermediate risk prostate cancer at 10-year followup (study did not report number of patients in this subgroup)	High	Consistency unknown (single study)	Direct	Imprecise HR 0.91 (0.80 to 1.04). Effect size was not statistically significant	Inconclusive evidence	Insufficient for all patient subgroups
	Prostate cancer-specific mortality among men with high risk prostate cancer at 10-year followup (study did not report number of patients in this subgroup)	High	Consistency unknown (single study)	Direct	Precise HR 0.59 (0.50 to 0.60). Effect size was statistically significant	Inconclusive evidence	Insufficient for patient subgroup
Conservative management vs. ADT[36]	All-cause mortality rate per 100 among men with poorly-differentiated prostate cancer [N=4,303] at 81-month followup	High	Consistency unknown (single study)	Direct	Imprecise HR 1.04 (95% CI, 0.97 to 1.13). Effect size was not statistically significant	Inconclusive evidence	Insufficient for patient subgroup
	All-cause mortality rate per 100 among men with moderately-differentiated prostate cancer [N=14,660] at 81-month followup	High	Consistency unknown (single study)	Direct	Precise HR 1.15 (95% CI, 1.10 to 1.21). Effect size was statistically significant	Inconclusive evidence	Insufficient for patient subgroup
	Prostate cancer-specific mortality rate per 100 among men with poorly-differentiated prostate cancer [N=4,303] at 81-month followup	High	Consistency unknown (single study)	Direct	Imprecise HR 1.12 (95% CI, 0.96 to 1.29). Effect size was not statistically significant	Inconclusive evidence	Insufficient for patient subgroup
	Prostate cancer-specific mortality rate per 100 among men with moderately-differentiated prostate cancer [N=14,660] at 81-month followup	High	Consistency unknown (single study)	Direct	Imprecise HR 1.83 (95% CI, 1.58 to 2.12). Effect size was statistically significant	Inconclusive evidence	Insufficient for patient subgroup

Discussion

Key Findings and Strength of Evidence

This comparative effectiveness review (CER) update is intended to address four key questions (KQs) described in the Introduction section. Twenty-seven studies (32 publications) met the inclusion criteria for review for KQ 1. Six of the 27 studies also met the inclusion criteria for KQ 2, and 8 of the studies met the inclusion criteria for KQ 4. Studies that addressed KQ1 reported data for patient-oriented outcome measures such as overall survival, all-cause mortality, prostate cancer-specific mortality, quality of life, and adverse events. Evidence addressing KQ 2 or KQ 4 came solely from subgroup analyses of some larger studies that addressed KQ 1. Although these subgroup analyses reported data on overall survival, all-cause mortality, or prostate cancer-specific mortality for specific patient subgroups, they did not report adverse events that occurred in these subgroups.

Table 33 summarizes our findings on the patient-oriented health outcomes from randomized controlled trials (RCTs) for KQ 1. These outcomes include overall survival, all-cause mortality, prostate cancer–specific mortality, and quality of life (QOL; reported using a global QOL score), for which we have assessed the strength of evidence (SOE). The findings on other reviewed outcomes were provided in the Results section and also appear in Appendix G.

Table 33 includes four comparisons of interventions. For the comparison of radical prostatectomy (RP) versus watchful waiting (WW), the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial reported data on all-cause and prostate cancer–specific mortalities at the end of the 15-year followup period, and the finding favors RP with a low SOE grade. Both the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the SPCG-4 trial reported data on all-cause and prostate cancer–specific mortalities at the end of the 12-year followup period, but we found the evidence on this outcome was insufficient to draw any conclusion. Neither study compared RP to active surveillance.

We did not combine both studies because the PIVOT[16] and SPCG-4[25] enrolled different populations. In comparison to the SPCG-4 trial, the PIVOT study enrolled a higher percentage of men with non-palpable tumors and low PSA values. The SPCG-4 trial began in 1989 when PSA screening was not widespread. Although the trial's eligibility criteria was T1 or T2, these tumors were typically understaged. Following RP, nearly half of the patients in the SPCG-4 trial compared with about 15 percent of patients in the PIVOT study had extracapsular extension (pT3, tumor extending beyond capsule). Additionally, the protocol for the WW arms differed between these studies. In the SPCG-4 trial, transurethral resection of the prostate (TURP) was recommended as the initial treatment for men with urinary obstruction, and hormonal treatment was recommended for men with disseminated disease (before January 2003) or as the patient's physician advised it (after January 2003). In the PIVOT study, patients with symptomatic local progression are treated first with alpha blockers or mechanical intervention (e.g., TURP). Hormonal therapy is considered first-line therapy for patients with disease progression requiring nonmechanical therapy. Patients with disease that continues to progress or fails to respond to hormonal therapy underwent radiotherapy or chemotherapy. In the PIVOT study, patients with symptomatic local disease progression despite mechanical therapy and alpha blockers may also undergo prostatectomy.

The evidence on QOL based on the PIVOT[16] and SPCG-4[25] trials is also insufficient to permit conclusions.

We note that these findings should always be interpreted with caution. Their applicability will be further discussed in the following sections. Furthermore, to make this review reasonably concise, outcomes that are not labeled as "major health outcomes" as aforementioned are not summarized in Table 33. However, the findings on these outcomes can be important and provide useful input to clinical decision making.

For example, a significant reduction was found in risk of development of metastatic disease in men who underwent surgery in the SPCG-4 trial (not summarized in Table 33, but reported in evidence Table 62 in Appendix G).[25] Although this is not a QOL assessment, it has serious QOL implications because bone metastasis is a significant determinant of QOL in men with prostate cancer.

The findings of the 2008 report that this current review updates are primarily based on the SPCG-4 and another small trial.[13] The 2008 report found that men with clinically localized prostate cancer detected by methods other than PSA testing and treated with RP experienced fewer deaths from prostate cancer, marginally fewer deaths from any cause, and fewer distant metastases.

For the comparison of radical retropubic prostatectomy versus brachytherapy, the evidence on the only reported outcome, QOL at 1 year, is insufficient for drawing any conclusion. The 2008 report did not identify any evidence from RCTs that addressed the same comparison.[13]

For the comparison of external beam radiotherapy (EBRT) alone versus EBRT combined with androgen-deprivation therapy (ADT), the data on overall survival, all-cause mortality, and prostate cancer–specific mortality reported in the trials favor the combined treatments with a low SOE grade. However, these findings should be interpreted with a thorough consideration of the specific patient populations and the treatment methods used in the trials. For example, treating low-risk patients with EBRT plus ADT would be considered substantial overtreatment by most national clinical guidelines. The D'Amico study did not include these patients and the Jones study found no difference in this subgroup.[24,26] Additionally, the radiation dose in both of these trials was low, and the length of ADT (only 4 months) might be too short for patients with high-risk disease. The applicability of these trials will be further discussed in the following sections.

The 2008 report reviewed two RCTs that compared the same pair of interventions.[13] One found that EBRT plus ADT reduced all-cause and disease-specific mortalities compared with EBRT alone after a median followup of 4.5 years. The other one found that, compared with EBRT alone, EBRT plus ADT did not significantly reduce disease-specific mortality in subjects with T2b and T2c cancer but reduced any-cause death in subjects with T2c disease. Overall, the low or insufficient SOE grades and inconsistent findings in the existing evidence suggest that the comparative effectiveness of EBRT versus EBRT plus ADT is still uncertain and will need future studies for validation.

For the comparison of ADT versus ADT in combination of EBRT, the evidence on the only reported major outcome, prostate cancer–specific mortality, is insufficient for drawing any conclusion. The 2008 report did not identify any evidence from RCTs that addressed the same comparison.[13]

Table 34 is a summary of the findings from the reviewed nonrandomized comparative studies that reported on at least one of the aforementioned major health outcomes. Regardless of the selection bias embedded in this type of study, we included them in this current review primarily to supplement what is missing in the RCT-based evidence. Our review found that the SOE is insufficient for drawing any conclusion for any treatment comparisons performed in these nonrandomized studies. The main reasons for the insufficient SOE gradings include the high risk

of bias of the individual studies included in the evidence base and the small number of studies addressing each treatment/outcome comparison.

Finally, because adverse-event definitions and severity varied widely across the included studies, we did not perform an assessment of the comparative effectiveness on adverse events of localized prostate cancer treatments. However, we reported individual data on harms as presented by study authors (see Table 66 and Table 67). Adverse events such as urinary incontinence, bowel incontinence, and erectile dysfunction were mostly reported among men who underwent RP. Conversely, adverse events such as genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction were reported among men who received radiation therapy.

Table 33. Summary of the main findings from randomized controlled trials for Key Question 1

Evidence Base	Comparison	Patient-oriented Outcomes	Findings	SOE Grade
SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality at 15 years	Favors RP RR 0.75; 95% CI, 0.61 to 0.92	Low
SPCG-4 trial, 2011[25]	RP vs. WW	PCSM at 15 years	Favors RP RR 0.62; 95% CI, 0.44 to 0.87	Low
SPCG-4 trial, 2011[25] and PIVOT, 2012[16]	RP vs. WW	All-cause mortality at 12 years	Inconclusive SPCG-4 trial: no significant difference between the interventions PIVOT: no significant difference between the interventions	Insufficient
SPCG-4 trial, 2011[25] and PIVOT, 2012[16]	RP vs. WW	PCSM at 12 years	Inconclusive SPCG-4 trial: favors RP RR 0.65, 95% CI, 0.45 to 0.94 PIVOT: no significant difference between the interventions	Insufficient
SPCG-4 trial, 2011[25]	RP vs. WW	QOL (median followup of 12.2 years)	Inconclusive	Insufficient
Giberti et al., 2009[21]	Radical retropubic prostatectomy vs. brachytherapy	QOL at 1 or 5 years	Inconclusive	Insufficient
Jones et al., 2011[26] and D'Amico et al., 2008[24]	EBRT vs. EBRT plus ADT	Overall survival	Favors EBRT plus ADT The finding from the included studies were statistically significant in the same direction	Low
D'Amico et al., 2008[24]	EBRT vs. EBRT plus ADT	All-cause mortality (median followup of 7.6 years)	Favors EBRT plus ADT Hazard ratio 1.8 (95% CI, 1.1 to 2.9)	Low
Jones et al., 2011[26] and D'Amico et al., 2008[24]	EBRT vs. EBRT plus ADT	PCSM	Favors EBRT plus ADT The findings from the included studies were statistically significant in the same direction	Low

Table 33. Summary of the main findings from randomized controlled trials for Key Question 1 (continued)

Evidence Base	Comparison	Patient-oriented Outcomes	Findings	SOE Grade
Widmark et al., 2009[23]	ADT vs. EBRT plus ADT	PCSM at 10 years	Inconclusive	Insufficient

For the interpretation of SOE grade, refer to AHRQ's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews"[48]

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; QOL=quality of life; RP=radical prostatectomy; RR=relative risk; SOE=strength of evidence; SPCG-4=Scandinavian Prostate Cancer Group-4; WW=watchful waiting.

Table 34. Summary of the main findings from nonrandomized comparative studies for Key Question 1

Evidence Base	Comparison	Patient-oriented Outcomes	Findings	SOE Grade
Abdollah et al., 2012[32]	Radiotherapy vs. observation	PCSM at 10-year followup	Inconclusive	Insufficient
Kibel et al., 2012[31]	RP vs. 3D-CRT plus intensity-modulated radiation therapy vs. BT	Overall survival and PCSM at 10 year followup	Inconclusive	Insufficient
Rosenberg et al., 2012[33]	BT plus EBRT vs. BT plus ADT	PCSM at 4.4- and 4.8-year followup for the 2 treatment cohorts, respectively	Inconclusive	Insufficient
Shen et al., 2012[42]	BT vs. EBRT vs. BT plus EBRT	PCSM after a median followup of 6.4 years	Inconclusive	Insufficient
Abdollah et al., 2011[49]	RP vs. observation	PCSM and other-cause mortality at 10-year followup	Inconclusive	Insufficient
Hadley et al., 2010[38]	RP vs. conservative management	All-cause mortality and PCSM	Inconclusive	Insufficient
Dosoretz et al., 2010[41]	BT vs. BT plus ADT	All-cause mortality after a median followup of 4.8 years	Inconclusive	Insufficient
Lu-Yao et al., 2008[36]	Primary ADT vs. conservative management	Overall and prostate cancer–specific survival and mortality after a median followup of 81 months	Inconclusive	Insufficient
Krambeck et al., 2008[28]	Radical retropubic prostatectomy vs. robotic-assisted radical prostatectomy	QOL, PCSM, and other-cause mortality after a median followup of 1.3 years	Inconclusive	Insufficient
Albertsen et al., 2007[43]	Surgery vs. radiation vs. observation	PCSM survival and overall survival at 13-year followup	Inconclusive	Insufficient
Ferrer et al., 2008[30]	RP vs. 3D-CRT vs.BT	QOL at 2-year followup	Inconclusive	Insufficient

3D-CRT=Three-dimensional conformal radiation therapy; ADT=androgen-deprivation therapy; BT=brachytherapy; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; RP=radical prostatectomy.

For KQ 2, two RCTs that compared RP versus WW and another two RCTs that compared EBRT alone versus EBRT plus ADT performed subgroup analysis according to patient characteristics.

For the comparison of RP versus WW, both RCTs analyzed data stratified by age. The PIVOT study found no significant difference in all-cause or cancer-specific mortality between RP and WW for the age groups of younger than 65 years and 65 years and older.[25] We note that the PIVOT trial was designed to recruit 2,000 patients and fell far short of that number, enrolling 731. This may have an impact on the results of the study, particularly for the subgroup analyses. The SPCG-4 trial found a significant advantage of RP over WW in all-cause and cancer-specific mortalities for patients younger than 65 years of age but not for the patient group of 65 years and older.[16] The PIVOT study also performed subgroup analysis according to race and self-reported performance status. No difference was found in all-cause or cancer-specific mortality between RP and WW for any race or performance score category that was analyzed.[25]

For the comparison of EBRT alone versus EBRT plus ADT, one RCT found that for patients with no comorbidity or a minimal comorbidity score, EBRT plus ADT was associated with a significantly higher 8-year survival than EBRT alone.[24] However, for patients with a moderate or severe comorbidity score, overall survival was not significantly different between the two intervention groups. The other RCT found no statistical evidence of a differential benefit between whites and blacks or between age subgroups (younger than 70 years of age vs. 70 years or older) in overall 10-year survival and prostate cancer–specific mortality.

The only RCT reviewed in the 2008 report that performed a subgroup analysis according to any patient characteristics is the SPCG-4 trial. The subgroup analysis of the earlier SPCG-4 trial data found that the difference in prostate cancer mortality between RP and WW appeared to be primarily in patients younger than 65 years.[13] The findings from the RCTs on KQ 2 are summarized in Table 35. Overall, these RCTs reviewed in the current review and in the 2008 report were not well-powered to detect statistical significance in patient-oriented outcomes in subgroup analyses. The strength of this RCT-based evidence body is insufficient for us to draw any conclusion for KQ 2.

In addition to the RCTs, two nonrandomized comparative studies were also reviewed for KQ2 (summarized in Table 36). The strength of the non-RCT-based evidence is also insufficient for drawing any conclusion for KQ 2. None of the included studies—RCTs and non-RCTs—reported adverse events for KQ 2 based on patient characteristics.

Table 35. Summary of the findings from randomized controlled trials for Key Question 2

Evidence Base	Comparison	Outcome	Patient Characteristics by Which Data Were Stratified	Findings	SOE Grade
PIVOT, 2012[16] and SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality and PCSM	Age	Inconclusive	Insufficient for patient subgroup
PIVOT, 2012[16]	RP vs. WW	All-cause mortality and PCSM	Race, self-reported performance status	Inconclusive	Insufficient for patient subgroup
D'Amico et al., 2008[24]	EBRT vs. EBRT plus ADT	8-year overall survival	Comorbidity scores	Inconclusive	Insufficient for patient subgroup

Table 35. Summary of the findings from randomized controlled trials for Key Question 2 (continued)

Evidence Base	Comparison	Outcome	Patient Characteristics by Which Data Were Stratified	Findings	SOE Grade
Jones et al., 2011[26]	EBRT vs. EBRT plus ADT	10-year overall survival and PCSM	Age, race	Inconclusive	Insufficient for patient subgroup

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; RP=radical prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4; WW=watchful waiting.

Table 36. Summary of the findings from nonrandomized comparative studies for Key Question 2

Evidence Base	Comparison	Outcome	Patient Characteristics by Which Data Were Stratified	Findings	SOE Grading
Dosoretz et al., 2010[41]	Brachytherapy vs. Brachytherapy plus	All-cause mortality at a median followup of 4.8 years	Age	Inconclusive	Insufficient for patient subgroup
Abdollah et al., 2012[32]	Observation vs. androgen deprivation therapy	Prostate cancer–specific mortality at 10-year followup	Age, Charlson comorbidity score	Inconclusive	Insufficient for patient subgroup

For KQ 3, we did not identify any comparative study that directly examined how provider characteristics influence the effectiveness of different treatments. As a result, this current review does not add new information to that reported in the 2008 report on the same KQ.

For KQ 4, two RCTs that compared RP and WW and another RCT that compared EBRT alone versus EBRT plus ADT performed subgroup analysis according to tumor characteristics. None of the included studies reported adverse events for KQ 4 based on tumor characteristics.

For the comparison of RP versus WW, both RCTs analyzed data stratified by PSA level. The PIVOT study found that RP did not reduce all-cause or prostate cancer–specific mortality among men with PSA of less than 10 ng/mL, but resulted in a significant reduction in the mortalities among men with PSA of more than 10 ng/mL.[25] However, the SPCG-4 trial found that the PSA level (less than 10 ng/mL vs. 10 ng/mL or more) did not affect the superiority of RP in reducing all-cause or prostate cancer–specific mortality.[16] Although their findings differ for patients with PSA less than 10 ng/mL, the two trials show some overlap in findings (reduced mortality with RP) for the subgroup of patients with PSA greater than 10 ng/mL.

With respect to tumor risk levels, the PIVOT study found that in comparison to WW, RP led to a significant reduction in all-cause mortality among patients with intermediate tumor risk (based on PSA, Gleason score, or tumor stage) but not in high- or low-risk patients. However, the SPCG-4 trial found a significant reduction in overall mortality (but not prostate cancer–specific mortality) associated with RP in low-risk patients (based on PSA level less than 10 ng/mL and Gleason score less than 7 or a WHO of grade 1 in preoperative biopsy specimens) and no data was reported for men with high-risk cancer. The subgroup analysis for other tumor characteristics or outcomes reported in PIVOT and SPCG-4 trials suggests that those tumor characteristics did not significantly alter the comparative findings.

For the comparison of EBRT alone versus EBRT plus ADT, one RCT performed a subgroup analysis and found that adding short-term ADT to EBRT led to a significantly higher overall survival or prostate cancer–specific mortality among patients of intermediate tumor risk (based on PSA, Gleason score, or tumor stage) but not among patients with high- or low-risk cancer.[26] The findings from the RCTs on KQ 4 are summarized in Table 37.

The only RCT reviewed in the 2008 report that performed a subgroup analysis according to any tumor characteristics is the SPCG-4 trial. The subgroup analysis of the earlier SPCG-4 trial data concluded that disease-specific mortality at 10 years for men having RP compared with WW did not differ according to baseline PSA level or Gleason score.

Overall, the RCTs reviewed in the current review and in the 2008 report were not well-powered to detect statistical significance in patient-oriented outcomes in subgroup analyses, and even significant findings should be viewed as hypothesis-generating rather than definitive evidence. The strength of this RCT-based evidence body is insufficient to allow any conclusion for KQ 4. In addition to the RCTs, five nonrandomized comparative studies were also reviewed for KQ 4 (summarized in Table 38). The strength of the non-RCT-based evidence is also insufficient to allow any conclusion.

Table 37. Summary of the main findings from randomized controlled trials for Key Question 4

Evidence Base	Comparison	Outcome	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grade
PIVOT, 2012,[16] and SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality and PCSM	PSA	Inconclusive	Insufficient for patient subgroup
SPCG-4 trial, 2011[25]	RP vs. WW	All-cause mortality and PCSM	Gleason score	Inconclusive	Insufficient for patient subgroup
PIVOT, 2012[16]	RP vs. WW	All-cause mortality and PCSM	Risk level based on PSA, Gleason score, or tumor stage	Inconclusive	Insufficient for patient subgroup
SPCG-4 trial[25]	RP vs. WW	All-cause mortality and PCSM	Risk level based on PSA, Gleason score, or a WHO grade of 1	Inconclusive	Insufficient for patient subgroup
Jones et al., 2011[26]	EBRT vs. EBRT plus ADT	10-year overall survival and PCSM	Risk level based on PSA, Gleason score, or tumor stage	Inconclusive	Insufficient for patient subgroup

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; PSA=prostate-specific antigen; RP=radical prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4; WHO=World Health Organization; WW=watchful waiting.

Table 38. Summary of the main findings from non-randomized comparative studies for Key Question 4

Evidence Base	Comparison	Outcome	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grading
Dosoretz et al., 2010[41]	BT vs. BT plus ADT	All-cause mortality at a median followup of 4.8 years	PSA, Gleason score, and clinical T classification	Inconclusive	Insufficient for patient subgroup

Table 38. Summary of the main findings from non-randomized comparative studies for Key Question 4 (continued)

Evidence Base	Comparison	Outcome	Tumor Characteristics by Which Data Were Stratified	Findings	SOE Grading
Rosenberg et al., 2012[33]	BT plus EBRT vs. BT plus ADT	PCSM at median followup of 4.4 years and 4.8 years, respectively	PSA, Gleason score	Inconclusive	Insufficient for patient subgroup
Kibel et al., 2012[31]	RP vs. EBRT vs. BT	Overall survival and PCSM at 10-year followup	Tumor risk (high, intermediate, low)	Inconclusive	Insufficient for patient subgroup
Abdollah et al. 2012[32]	Observation vs. ADT	PCSM at 10-year followup	Tumor risk (high, intermediate, low)	Inconclusive	Insufficient for patient subgroup
Lu-Yao et al., 2008[36]	Conservative management vs. ADT	All-cause mortality and PCSM at 81-month followup	Tumor risk (poorly differentiated, moderately-differentiated)	Inconclusive	Insufficient for patient subgroup

ADT=Androgen-deprivation therapy; Brachytherapy=BT; EBRT=external beam radiation therapy; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; PSA=prostate-specific antigen; RP=radical prostatectomy

Applicability

The evidence-based conclusions are applicable only to the types of patients enrolled in the studies underlying those conclusions, the types of clinical settings in which the studies were conducted, the types of interventions being compared, and the particular outcomes and followup period reported. Table 39 is a summary of these factors that may restrict the applicability of the findings from the randomized controlled trials discussed in the previous section. Similar factors also affect the applicability of the findings from the 20 nonrandomized comparative studies included in this current review. These 20 studies compared a broad range of treatments for localized prostate cancer. The information about the patient population, clinical settings, compared treatment, and reported outcomes and followup duration for these nonrandomized studies are available in Table 49, Table 51, Table 53, Table 55, Table 57, Table 59, Table 61, Table 63, Table 65, and Table 67 in Appendices E through G.

While the restrictions on the applicability of the conclusions may vary across the evidence bases for different treatment comparisons, some restrictions may be common to most of these evidence bases. All of the RCTs included in this review recruited the patients before 2002. Since then, the treatment options compared in many studies have greatly evolved. For example, open surgery was the main treatment technique for radical prostatectomy in the reviewed RCTs. However, in recent years, robotic-assisted surgery has become the dominating technique for radical prostatectomy in the United States. Similarly for EBRT, brachytherapy, and other treatments, advances in technologies and knowledge have helped many of these treatments better target the cancer, improving the effectiveness of, and patient tolerance of the treatments. As a result, the evidence based on dated medical techniques may not apply to the current practice. Therefore, future studies of high quality are required for validating the comparative effectiveness and safety of the current and emerging treatment techniques (e.g., robotic-assisted surgery, proton beam, stereotactic body radiation therapy).

Additionally, the patients studied in the RCTs included in this review may have a different risk profile from the patients whose diagnosis of prostate cancer are established at the current time. Ten to 15 years ago, prostate cancers were primarily detected by digital rectal examination or in tissue specimens obtained during transurethral resection of the prostate for treating benign prostatic obstruction. Currently, the vast majority of prostate cancers detected in the United States are found due to PSA testing. Men often start to receive PSA tests in the 40s and continue taking the test on a regular basis until their 80s. As a result, the patients whose diagnosis is established nowadays can be younger and have more confined cancers than those studied in the reviewed RCTs, which further restricts the applicability of the reviewed evidence.

Because of the intensified concern about overdiagnosis of prostate cancer in recent years, the manner in which PSA testing is used for screening prostate cancer and the criteria for establishing an abnormal PSA test result may continue to change. Patient and tumor characteristics among men with prostate cancer diagnosed in the future are likely to be different from that of men diagnosed in the past and currently.

Implications for Clinical and Policy Decisionmaking

Despite the restricted applicability of the evidence, the current review may still inform some important treatment decisions that patients with localized prostate cancer face. Our review suggests that in comparison with watchful waiting, radical prostatectomy appears to lead to a reduced all-cause or cancer-specific mortality in at least some patients with localized prostate cancer after a 15-year followup.[25] However, the SOE from the SPCG-4 trial[25] is rated as Low (meaning that there is low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate of effect), and the evidence does not clearly identify the subgroup(s) of patients for which this finding is applicable. Our review was unable to draw any conclusion on global QOL. Therefore, it is unclear how patients as a whole can balance the trade-off between the potential benefit in long-term survival and the potential harms (e.g., urinary and bowel incontinence, sexual dysfunction) associated with the surgery. In the end, the treatment decision rests with each individual patient, his family, and his physicians. These stakeholders' personal preferences and values play a significant role in this decisionmaking process. This may particularly be true for patients with life expectancies of less than about 15 years.

This review and the 2008 report both attempted to evaluate whether a particular patient group (in terms of age, race, general health status, and various tumor risk factors) might benefit more from a compared intervention. Addressing this question would help patients and clinicians make better-informed treatment decision. However, the evidence reviewed does not provide any consistent conclusion on this issue. For example, the SPCG-4 trial found that RP led to significantly lower all-cause and cancer-specific mortalities compared with WW among patients younger than 65 years of age but not among the older patient group.[16] However, the PIVOT study did not have the same finding.[25]

On the other hand, the PIVOT study found that RP did not reduce all-cause or cancer-specific mortality among men with PSA of less than 10 ng/mL but resulted in a significant reduction among men with PSA of more than 10 ng/mL. However, this finding is only partly confirmed by the SPCG-4 trial, which found a mortality reduction with RP in both subsets of patients. Although their findings differ for patients with PSA less than 10 ng/mL, the two trials show some overlap in findings (reduced mortality with RP) for the subgroup of patients with PSA

greater than 10 ng/mL. Nevertheless, enough inconsistency remains in the evidence that clear guidance regarding the appropriate patient population for RP is difficult to establish.

This current review also reached some conclusions for the comparison of EBRT alone versus EBRT combined with ADT. The evidence based on the two RCTs[24,26] suggests that the results for overall survival and prostate cancer–specific mortality favored the combined treatments with a low SOE grade. The evidence also suggests that the advantage of EBRT combined with ADT may only occur among patients with no comorbidity or a minimal comorbidity score, who are white and younger than the age of 70 years. However, this evidence is weak and requires further validation by future studies before it can be used to form clinical guidance for choosing appropriate cases for the treatments. Similarly, the evidence for other treatment comparisons covered in the current review also need further validation, particularly via rigorously designed RCTs, to form a more reliable foundation for making clinical recommendations.

Table 39. Factors affecting the applicability of the evidence from randomized controlled trials

Trial, Setting, Enrollment Period	Population, Demographic, Disease State	Interventions and Comparators	Outcomes and Followup Time points
PIVOT[16] A multicenter RCT involving 731 men recruited from 52 medical centers (44 Veterans Affairs and 8 National Cancer Institute sites) across the United States. November 1994–January 2002	Age younger than 75 years, T1–T2NxM0, PSA <50 ng/mL	RP: The technique used was at the surgeon's discretion. Additional interventions were determined by each participant and his physician. Observation: Men in the watchful waiting study arm were offered palliative (noncurative) therapy (e.g., transurethral resection of the prostate for local progression causing urinary obstruction, androgen deprivation and/or targeted radiation therapy for evidence of distant spread).	All-cause mortality, PCSM, clinical progression, and adverse events Median followup: 10 years
SPCG-4 trial[25,46,47,54] A multicenter RCT involving 695 men conducted at 14 centers in Sweden, Finland, and Iceland. October 1989–December 1999	Age younger than 77 years, T1b, T1c, T2, PSA <50 ng/mL	RP: The surgical procedure started with a lymphadenectomy of the obturator fossa; if no nodal metastases were found in frozen sections, the RP was performed. Radical excision of the tumor was given priority over nerve-sparing surgery. WW: Men in the watchful waiting group who had signs of obstructive voiding disorders were treated with transurethral resection. Metastases detected by bone scan were managed with hormonal therapy.	All-cause mortality, PCSM, clinical progression, adverse events, and QOL Median followup: 15 years

Table 39. Factors affecting the applicability of the evidence from randomized controlled trials (continued)

Trial, Setting, Enrollment Period	Population, Demographic, Disease State	Interventions and Comparators	Outcomes and Followup Time points
Giberti et al., 2009[21] A single-center RCT involving 200 men was conducted in Italy. May 1999–October 2002	Caucasian men, T1c or T2a, PSA <10 ng/mL and Gleason sum <6)	RRP: Bilateral nerve-sparing RRP in accordance with Walsh's principles and standard lymph node dissection were performed on all the patients by a single surgeon. Brachytherapy was performed by a team that included a urologist, a radiation therapist, and a primary care physician, through a transperitoneal template-guided peripheral loading real-time technique and seeds of iIodine125. A D90>140 Gy was considered the cut-off value to predict a good-quality implant.	QOL, biochemical progression, adverse events 5 year followup
Jones et al., 2011[26] A multicenter phase 3 RCT involving 1,979 men was conducted in the United States and Canada. 1994–2001	Age younger than 71 years, T1b, T1c, T2a, T2b prostate adenocarcinoma, PSA <20 ng/mL	EBRT: Radiotherapy was administered in daily 1.8 Gy fractions prescribed to the isocenter of the treatment volume, consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate. EBRT plus short-term ADT: Flutamide at a dose of 250 mg orally 3 times a day and either monthly subcutaneous goserelin at a dose of 3.6 mg or intramuscular leuprolide at a dose of 7.5 mg for 4 months. Radiotherapy commenced after 2 months of ADT.	Overall survival, PCSM, clinical progression, adverse events, biochemical progression, and QOL Median followup: 9.1 years
Widmark et al., 2009[23] A multicenter RCT involving 875 men was conducted at 47 centers in Norway, Sweden, and Denmark. February 1996–December 2002	Age younger than 76 years, T1, T2, T3 PSA <70 ng/mL	ADT: patients received LHRH agonist, leuprorelin (Procren depot; 3.75 mg a months or 11.25 mg every 3 months), for 3 months and were simultaneously treated with 250 mg oral antiandrogen, flutamide 3 times a day. Flutamide was discontinued when antiandrogen treatment side effects occurred and then reinstituted with stepwise increased dose to at least 500 mg. If this failed, antiandrogen was changed to bicalutamide (150 mg once a day). ADT plus EBRT: ADT and a standard 3D conformal radiotherapy technique was applied with a prescribed central dose (of 50 Gy) to the prostate and seminal vesicles. A sequential boost of at least 20 Gy was added to the prostate, which received a total dose minimum of 70 Gy.	PCSM Median followup: 7.6 years

Table 39. Factors affecting the applicability of the evidence from randomized controlled trials (continued)

Trial, Setting, Enrollment Period	Population, Demographic, Disease State	Interventions and Comparators	Outcomes and Followup Time points
D'Amico et al., 2008[24] A single-center RCT involving 206 men was conducted in the United States. December 1, 1995–April 15, 2001	Patients with T1 or T2 tumors who had at least a 10-year life expectancy excluding death from prostate cancer	EBRT: Daily dose of 1.8 Gy for initial 25 treatments, totaling 45 Gy, and 2.0 Gy for final 11 treatments, totaling 22 Gy. EBRT plus ADT: EBRT plus ADT which consisted of a LHRH agonist, leuprolide or goserelin, and the antiandrogen flutamide. Leuprolide was delivered intramuscularly each month at a dose 7.5 mg or 22.5 mg every 3 months. Goserelin was administered subcutaneously each month at a dose of 3.6 mg or 10.8 mg every 3 months. Flutamide was taken orally at a dose of 250 mg every 8 hours and starting 1–3 days before leuprolide.	Overall survival, all-cause mortality, and PCSM Median followup: 7.6 years

ADT=Androgen-deprivation therapy; EBRT=external beam radiation therapy; Gy=gray; LHRH=luteinizing hormone–releasing hormone; PCSM=prostate cancer–specific mortality; PIVOT=Prostate Intervention Versus Observation Trial; PSA=prostate-specific antigen; QOL=quality of life; RCT=randomized controlled trial; RP=radical prostatectomy; RRP=radical retropubic prostatectomy; SPCG-4=Scandinavian Prostate Cancer Group-4.

Limitations of the Evidence Base

This current review has several limitations. First, although more RCTs were available for this review than for the 2008 report we are updating, the amount of evidence from well-designed RCTs that directly compare different treatments, particularly emerging technologies (e.g., proton beam therapy, HIFU), is still small. The few RCTs that met the inclusion criteria for the review compared only a few treatments (e.g., RP vs. WW, EBRT alone vs. EBRT plus ADT) of interest. Questions about the effectiveness and safety of new and emerging treatment methods are largely unanswered by RCTs.

Second, all of the reviewed RCTs were conducted more than 10 years ago. The manner in which PSA testing was used for detecting prostate cancer and the treatment techniques used may not reflect current practices, so the RCT results may not be generalizable to current practice settings. Third, there was little reporting of outcomes according to major patient and tumor characteristics. The reviewed RCTs that performed subgroup analyses according to patient or tumor characteristics often do not have adequate power to detect significant effects within the subgroups.

Fourth, wide variation existed in reporting and definitions of outcomes and tumor and patient characteristics, which make evidence synthesis difficult. Additionally, this review included only studies published in English. The review also used specific sample size cutoffs as a criterion to exclude small-sized studies. Inclusion of small-sized studies and those published in other languages may have resulted in additional conclusions or may have contradicted some conclusions. Furthermore, this review limited evidence to studies that reported for T1 and T2 disease separately from T3 or T4 disease. Studies that did not report data separately (e.g., reporting data for T1, T2, T3, and T4 disease together) were excluded. As a result, some information potentially relevant to the topic of this review may have been missed.

Research Gaps

To further address the KQs of this review, additional RCTs are needed. In Table 68 and Table 69 in Appendix H, we provide a summary of six ongoing clinical trials: four in the United States, one in Canada, and one in the United Kingdom (ProtecT [Prostate testing for cancer and Treatment] Study). Ideally, future RCTs should recruit patients with PSA-detected prostate cancer and compare patient-focused outcomes (e.g., all-cause and cancer-specific mortalities, QOL) between treatment options and techniques used in the current practice with a long followup. These RCTs should use standardized or validated methods to determine patient outcomes and have adequate power to detect significant treatment effect.

High-quality observational studies (e.g., cancer registries and large prospective cohort studies that appropriately adjust for baseline differences between the groups) may also provide useful evidence, particularly in cases in which large differences in outcomes might exist. Observational studies may help estimate treatment effectiveness in high priority patient and tumor subgroups that have not been adequately addressed in RCTs. Findings from observational studies may also help generate hypotheses and design better RCTs. We noted that some observational studies conflicted in their findings based on the analytic methods employed (e.g., propensity score versus instrumental variable approaches). Studies inconsistently defined and reported outcomes. Most of the existing evidence comes from nonrandomized comparative studies with treatment selection biases.

Finally, we did not identify any studies that compared active surveillance to current treatment therapies. Since watchful waiting or observation is not active surveillance, more studies are needed to assess the effectiveness of active surveillance. A major gap that we identified was the fact that since outcomes of surgery and radiation are influenced by center/surgeon volume and or expertise, most of these studies did not provide any information of practice of care that could have influenced the results in any of the included studies.

Conclusions

Overall, the body of evidence for the treatment of prostate cancer continues to evolve, but the evidence for most treatment comparisons is largely inadequate to determine comparative risks and benefits. Extended followup data from SPCG-4 and the recently published PIVOT trial add to our understanding of the effects of RP versus WW or observation in subgroups, but further clarification is needed. Neither study compared RP to active surveillance. The SOE on overall and prostate cancer–specific mortality from the SPCG-4 trial at 15-years followup are rated as low (i.e., low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate of effect) and favored RP in men with clinically detected localized prostate cancer. At 12-years followup, the evidence from the PIVOT and SPCG-4 trials on both outcomes is rated as insufficient. For the comparison of EBRT alone versus EBRT combined with ADT, the data on overall survival and prostate cancer–specific mortality reported in two trials favors the combined treatments with a low SOE grade. However, the patients most likely to benefit and the applicability of these findings to contemporary populations and practice remain questionable. Therefore, the findings from the surgical and radiotherapy trials should be interpreted with a thorough consideration of the specific patient populations and the treatment methods used in the trials. More RCTs that reflect contemporary practice and can control for many of the unknown and known confounding factors that can affect long-term outcomes are needed to evaluate comparative risks and benefits of a number of therapies for clinically localized prostate cancer.

Acronyms and Abbreviations

3D-CRT:	three-dimensional conformal radiotherapy
95% CI:	95 percent confidence interval
ADT:	androgen-deprivation therapy
AHRQ:	Agency for Healthcare Research and Quality (U.S. Department of Health and Human Services)
ARR:	absolute risk reduction
BT:	brachytherapy
CER:	comparative effectiveness review
EB-IGRT:	external beam image-guided radiation therapy
EBRT:	external beam radiotherapy
EORTC-QLQ:	European Organization for research and Treatment of Cancer Quality of Life Questionnaire
EPC:	Evidence-based Practice Center
ERSPC:	European Randomized Study of Screening for Prostate Cancer
Gy:	gray
HDR-EBRT:	high dose–rate external beam radiation therapy
HDS:	high dose rate
HIFU:	high-intensity focused ultrasound
HR:	hazard ratio
IMRT:	intensity-modulated radiation therapy
IQR:	interquartile range
KQ:	key question
LDR:	low dose rate
LHRH:	luteinizing hormone–releasing hormone
MRI:	magnetic resonance imaging
NIH:	National Institutes of Health
OR:	odds ratio
ORRP:	open retropubic radical prostatectomy
PCSM:	prostate cancer–specific mortality
PICOTS:	Population (patients), Intervention, Comparators, Outcomes, Timing, Setting
PIVOT:	Prostate Cancer Intervention Versus Observation Trial
PLCO:	Prostate, Lung, Colorectal, and Ovarian cancer screening trial
PSA:	prostate-specific antigen
QOL:	quality of life
RALP:	robotic-assisted laparoscopic prostatectomy
RALRP:	robotic-assisted laparoscopic radical prostatectomy
RARP:	robotic-assisted radical prostatectomy
RCT:	randomized controlled trial
RP:	radical prostatectomy
RR:	relative risk
RRP:	radical retropubic prostatectomy
SEER:	Surveillance Epidemiology and End Results (National Cancer Institute)
SF-36:	Short Form-36
SOE:	strength of evidence
SPCG-4:	Scandinavian Prostate Cancer Group-4

TEP:	Technical Expert Panel
TNM:	T (tumor) N (lymph node) M (metastases) classification system (American Joint Committee on Cancer)
TOO:	task order officer
TURP:	transurethral resection of the prostate
USPSTF:	U.S. Preventive Services Task Force
WW:	watchful waiting

Note: Acronyms and abbreviations used appendix tables are defined within the tables in which they appear.

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Appendix A. Literature Search Methods

Electronic Database Searches

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for the bibliographic databases appear below.

Table 40. Electronic database searches

Name	Date Limits	Platform/Provider
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	1/01/07–1/23/13	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	2007 through current	OVID
MEDLINE	2007 through current	OVID
PubMed	2007 through current	www.pubmed.gov
ClinicalTrials.gov	1/01/07–4/17/13	NIH

Detailed search strategies are presented below.

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.) Select manufacturer websites and a number of organization websites were searched for relevant information, including: ECRI Institute members' website, CDC, National Cancer Institute, and the American Cancer Society.

Medical Subject Headings (MeSH, EMTREE and Keywords)

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the concepts shown in the Topic-specific Search Terms table.

Table 41. Topic-specific search terms

Concept	Controlled Vocabulary	Keywords
Prostate cancer	EMBASE (EMTREE) Neoplasms/ Prostate/ Prostatic Neoplasms/ MeSH (PubMed) Neoplasms Prostate Prostatic Neoplasms	Cancer* Carcinoma* Neoplasm* Prostat*

Table 41. Topic-specific search terms (continued)

Concept	Controlled Vocabulary	Keywords
Treatment options	EMBASE (EMTREE) Brachytherapy/ Cryosurgery/ Cryotherapy/ Freezing/ High-Intensity Focused Ultrasound Ablation/ Prostatectomy/ exp Radiotherapy/ Watchful Waiting/ MeSH (PubMed) Brachytherapy Cryosurgery Cryotherapy Freezing High-Intensity Focused Ultrasound Ablation Prostatectomy exp Radiotherapy Watchful Waiting	Active surveillance Androgen deprivation Brachytherap* Cryoablat* Cryosurger* Cryotherap* Curietherap* EBRT Freez* HIFU High intensity focused ultrasound IMRT LRP Prostatectom* Proton Radiotherap* Radiation RLRP Watchful waiting

Search Strategies

The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE AND MEDLINE. A similar strategy was used to search the databases comprising the Cochrane Library.

OVID Conventions:

$ or * = truncation character (wildcard)

ADJ*n* = search terms within a specified number (*n*) of words from each other in any order

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

Table 42. EMBASE/MEDLINE—OVID syntax

Set #	Concept	Search Statement
1	Prostate cancer	Prostatic Neoplasms/
2	Prostate cancer	(prostat$.ti,ab. or Prostate/) AND (cancer.ti,ab. or Neoplasms/ or neoplasm$ or carcinoma$)
3	Combine sets	S1 OR S2
4	Treatment options	watchful waiting.ti,ab. or Watchful Waiting/ or active surveillance.ti,ab. or prostatectom$.ti,ab. or Prostatectomy/ or LRP.ti,ab. or RLRP.ti,ab. or exp Radiotherapy/ or radiotherap$.ti,ab. or EBRT.ti,ab. or IMRT.ti,ab. or proton.ti,ab. or brachytherap$.ti,ab. or Brachytherapy/ or curietherap$.ti,ab. or cryosurger$.ti,ab. or Cryosurgery/ or cryotherap$.ti,ab. or Cyberknife.ti,ab. or Cryotherapy/ or cryoablat$.ti,ab. or Freezing/ or freez$.ti,ab. or androgen deprivation.ti,ab. or High-Intensity Focused Ultrasound Ablation/ or high intensity focused ultrasound.ti,ab. or HIFU.ti,ab. or (high and intensity and focused and ultrasound).ti,ab.
5	Publication types	(Randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp clinical trial/ or exp comparative study/ or cohort analysis or followup studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or followup studies/ or case series.ti,ab. or random$.hw. or random$.ti. or placebo$.ti,ab. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)).ti,ab. or latin square.ti,ab. or ISRCTN$.ti,ab. or ACTRN$.ti,ab. or (NCT$ not NCT).ti,ab.)
6	Combine sets	S3 AND S4 AND S5
7	Limit	6 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
8	Limit	7 not (book/ or edited book/ or case report/ or case reports/ or comment/ or conference abstract/ or conference paper/ or conference review/ or editorial/ or letter/ or news/ or note/ or proceeding/ or (book or edited book or case report or case reports or comment or conference or editorial or letter or news or note or proceeding).pt. or (“comment/reply” or editorial or letter or review-book).pt.)
9	Limit	8 not (case report.de. OR case reports.pt. OR case report.ti. OR (year ADJ old).ti,ab.)
10	Limit	Limit 9 to English and humans
11	Limit	Limit 10 to yr=“ 2007 - 2013”
12	Remove duplicates	Remove duplicates from 11 13
13	Limit	12 and compar$.ti,hw.
14	Limit	12 and (clinically adj local$)
15	Limit	12 and (stage 1 or stage one)
16	Limit	12 and (early adj3 stage)
17	Limit	12 and (nonmetastatic or non-metastatic)
18	Limit	12 and (gleason 7 or gleason score 7 or gleason 6 or gleason score 6)
19	Combine	13 or 14 or 15 or 16 or 17 or 18

Additional Conventions:

PubMed

* = truncation character (wildcard)

[tiab] = limit to title or abstract

Cochrane Library

* = truncation character (wildcard)

Menu-driven

Table 43. PubMed

Set #	Concept	Search Statement
1	Prostate cancer	prostat*[tiab] AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab])
2	Treatment options	"watchful waiting"[tiab] OR "active surveillance"[tiab] OR LRP[tiab] OR RLRP[tiab] OR prostatectom*[tiab] OR radiotherap*[tiab] OR EBRT[tiab] OR IMRT[tiab] OR proton[tiab] OR (intensity[tiab] AND modulated[tiab] AND therap*[tiab]) OR brachytherap*[tiab] OR curietherap*[tiab] OR cryosurger*[tiab] OR cryotherap*[tiab] OR cryoablat*[tiab] OR Cyberknife[tiab] OR freezing[tiab] OR "androgen deprivation"[tiab] OR HIFU[tiab] OR (high[tiab] AND intensity[tiab] AND focused[tiab] AND ultrasound*[tiab])
3	Publication types	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR comparative study[pt] OR evaluation studies [pt] OR meta-analysis[pt] OR multicenter study[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR comparative study [tw] OR comparative studies [tw] OR evaluation study[tw] OR evaluation studies [tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square" OR placebo* OR random* OR "control group" OR prospective* OR retrospective* OR volunteer* OR sham OR "meta-analysis"[tw] OR cohort OR ISRCTN* OR ACTRN* OR NCT*)
4	Combine sets	1 AND 2 AND 3
5	Limit	4 AND ("in process"[sb] OR publisher[sb] OR pubmednotmedline[sb])
6	Limit	Limit 5 to: Publication date from 2007/01/01 to 2013/12/31

Table 44. Cochrane Library

Set #	Concept	Search Statement
1	Prostate cancer	prostat* AND (neoplasm* OR cancer* OR carcinoma*)
2	Treatment options	"watchful waiting" OR "active surveillance" OR LRP OR RLRP OR prostatectom* OR radiotherap* OR EBRT OR IMRT OR proton OR (intensity AND modulated AND therap*) OR brachytherap* OR curietherap* OR cryosurger* OR cryotherap* OR cryoablat* OR Cyberknife OR freezing OR "androgen deprivation" OR HIFU OR (high AND intensity AND focused AND ultrasound*)
3	Combine sets	1 AND 2
4	Limit	Limit 3 to: Publication date from 2007 to 2013

Appendix B. Forms Used for Title, Abstract, and Full-Length Article Review

Table 45. Questions used for title, abstract, and full-length article review

Review Level	Questions	Answer Choices
Title screening	Is this article written in English?	Yes
		No
	Is this a study of human patients?	Yes, humans
		No, animal study
		No, in vitro or laboratory study or treatment planning study
		Systematic review or useful narrative review or guideline
		Review article without any additional information
		Study already excluded in the 2008 report
		Unsure
	Is this article about treating patients with localized prostate cancer?	Yes
		No, clearly off topic
		Outside our search date of 2007–current
		Unsure
Abstract screening	Studies conducted from 2007–current date	Yes
		No
		Already excluded in the 2008 report
	Does the study address one of the key questions?	Yes
		No
		Unsure
	Does the study evaluate one of the treatments of interest?	Yes
		No
		Unsure
	Does the study evaluate one of the treatments of interest?	Yes
		No
		Unsure
	For SYSTEMATIC REVIEWS/NARRATIVE REVIEWS/GUIDELINES only Is this a systematic review, narrative review of interest, or guideline of interest?	Yes
		No
		Unsure

Table 45. Questions used for title, abstract, and full-length article review (continued)

Review Level	Questions	Answer Choices
Article Screening	Does this study address KQ1 or KQ3? Key Question 1. What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer? (See list of therapies under KQ2 right below.) Key Question 3.How do provider/hospital characteristics affect outcomes of these therapies for overall and differentially (e.g., geographic region, case volume, learning curve)? If the study addresses KQ3, select KQ3 and HIT SUBMIT. Do not answer the rest of the questions. If you answer NO, neither question, you can also hit submit and skip the rest of the questions.	KQ 1 KQ 3 Neither KQ1 nor KQ3 Unsure
	Does this study address KQ1 or KQ3? If the study addresses KQ3, select KQ3 and HIT SUBMIT. Do not answer the rest of the questions. If you answer NO, neither question, you can also hit submit and skip the rest of the questions.	Yes No Unsure
	What patient population is enrolled or under study?	Localized prostate cancer (T1 and/or T2 only) Mixed group (T1, T2, T3, T4) Locally advanced prostate cancer or T3 or T4 only Metastatic prostate cancer Recurrent prostate cancer Castration-resistant prostate cancer Can't tell from abstract
	What kind of publication is this?	A clinical study A systematic review A narrative review or guideline Simulation model Unsure
	What outcome(s) is the study reporting? Check any that apply	Mortality Survival Quality of life Biochemical recurrence Progression to metastases Progression free survival Adverse events of treatment Unsure None of the above
	Is this a systematic review reporting on adverse events of treatments	Yes No Unsure

Table 45. Questions used for title, abstract, and full-length article review (continued)

Review Level	Questions	Answer Choices
Article Screening (continued)	What treatments is this article about? check any that apply	Watchful waiting/observation/active surveillance
		Radical prostatectomy
		External beam radiotherapy
		Interstitial brachytherapy
		Androgen deprivation therapy
		Cryotherapy
		High-intensity focused ultrasound therapy
		Proton therapy
		Unsure
		None of the above
	Is this a large comparative study comparing different treatment options of interest?	Yes, RCT with ≥100 patients per treatment arm
		Yes, nonrandomized comparative study with ≥500 patients per treatment arm
		Yes, nonrandomized comparative study with ≥500 patients per treatment arm
		Unsure
		None of the above
	Should this study be excluded for any other reasons? If so please explain.	Yes:

Appendix C. Full-Length Review Excluded Studies

Randomized controlled trials (RCTs) with a mixed population (≥15% of patient population had T3/T4 and did no separate data reported for T1 or T2)

Dearnaley DP, Sydes MR, Langley RE, et al. The early toxicity of escalated versus standard dose conformal radiotherapy with neo-adjuvant androgen suppression for patients with localised prostate cancer: results from the MRC RT01 trial (ISRCTN47772397). Radiother Oncol. 2007 Apr;83(1):31-41. PMID: 17391791

Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer. 2010 Jan 15;116(2):323-30. PMID: 19937954

Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol. 2012 May;103(2):217-22. PMID: 22341794

Mottet N, Peneau M, Mazeron J. Impact of radiotherapy (RT) combined with androgen deprivation (ADT) versus ADT alone for local control in clinically locally advanced prostate cancer. J Clin Oncol. 2010;28:abstract 4505.

Pollack A, Walker G, Buyyounouski M, et al. Five year results of a randomized external beam radiotherapy hypofractionation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2011;81:S1.

Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. Cancer. 2009 Oct 15;115(20):4695-704. PMID: 19691092

Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol. 2010 May;57(5):836-42. PMID: 19962227

Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011 Dec 17;378(9809):2104-11. PMID: 22056152

Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet. 2009 Jan 24;373(9660):301-8. PMID: 19091394

RCTs with <100 patients per treatment arm

D'Amico AV, Chen MH, Renshaw AA, et al. Risk of prostate cancer recurrence in men treated with radiation alone or in conjunction with combined or less than combined androgen suppression therapy. J Clin Oncol. 2008 Jun 20;26(18):2979-83. PMID: 18565884

Mason M, Maldonado Pijoan X, Steidle C, et al. Neoadjuvant Androgen. Clin Oncol (R Coll Radiol). 2012 Dec 17. PMID: 23257248

RCTs published outside search date

Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol. 2003 Nov 1;21(21):3972-8. PMID: 14581419

Nonrandomized comparative studies (N ≥500) without any attempt to control for selection bias using an acceptable method

Abdollah F, Schmitges J, Sun M, et al. Comparison of mortality outcomes after radical prostatectomy versus radiotherapy in patients with localized prostate cancer: a population-based analysis. Int J Urol. 2012 Sep;19(9):836-44.

Abdollah F, Sun M, Schmitges J, et al. Survival benefit of radical prostatectomy in patients with localized prostate cancer: estimations of the number needed to treat according to tumor and patient characteristics. J Urol. 2012 Jul;188(1):73-83. PMID: 22578732

Abdollah F, Sun M, Thuret R, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. Eur Urol. 2011 Jan;59(1):88-95. PMID: 20965646

Abern MR, Dude AM, Tsivian M, et al. The characteristics of bladder cancer after radiotherapy for prostate cancer. Urol Oncol. 2012 May 8. PMID: 22575239

Aizer AA, Yu JB, Colberg JW, et al. Radical prostatectomy vs. intensity-modulated radiation therapy in the management of localized prostate adenocarcinoma. Radiother Oncol. 2009 Nov;93(2):185-91. PMID: 19800702

Akita H, Okamura T, Ando R, et al. Implications of greater short-term PSA recurrence with laparoscopic as compared to retropubic radical prostatectomy for Japanese clinically localized prostate carcinomas. Asian Pac J Cancer Prev. 2011;12(11):2959-61. PMID: 22393971

Albers P, Schafers S, Lohmer H, et al. Seminal vesicle-sparing perineal radical prostatectomy improves early functional results in patients with low-risk prostate cancer. BJU Int. 2007 Nov;100(5):1050-4. PMID: 17760889

Alibhai SM, Leach M, Warde P. Major 30-day complications after radical radiotherapy: a population-based analysis and comparison with surgery. Cancer. 2009 Jan 15;115(2):293-302. PMID: 19025976

Arvold ND, Chen MH, Moul JW, et al. Risk of death from prostate cancer after radical prostatectomy or brachytherapy in men with low or intermediate risk disease. J Urol. 2011 Jul;186(1):91-6. PMID: 21571341

Abdel-Wahab M, Reis IM, Hamilton K. Second primary cancer after radiotherapy for prostate cancer--a seer analysis of brachytherapy versus external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2008 Sep 1;72(1):58-68. PMID: 18374503

Bhojani N, Capitanio U, Suardi N, et al. The rate of secondary malignancies after radical prostatectomy versus external beam radiation therapy for localized prostate cancer: a population-based study on 17,845 patients. Int J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):342-48.

Bittner N, Merrick GS, Galbreath RW, et al. Primary causes of death after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2008 Oct 1;72(2):433-40. PMID: 18448268

Carlsson S, Nilsson AE, Schumacher MC, et al. Surgery-related complications in 1253 robot-assisted and 485 open retropubic radical prostatectomies at the Karolinska University Hospital, Sweden. Urology. 2010 May;75(5):1092-7. PMID: 20022085

Colberg JW, Decker RH, Khan AM, et al. Surgery versus implant for early prostate cancer: results from a single institution, 1992-2005. Cancer J. 2007 Jul-Aug;13(4):229-32. PMID: 17762756

Cooperberg MR, Vickers AJ, Broering JM, et al. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer. 2010 Nov 15;116(22):5226-34. PMID: 20690197

Crook JM, Gomez-Iturriaga A, Wallace K, et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. J Clin Oncol. 2011 Feb 1;29(4):362-8. PMID: 21149658

Deutsch I, Zelefsky MJ, Zhang Z, et al. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. Brachytherapy. 2010 Oct-Dec;9(4):313-8. PMID: 20685176

Dosoretz AM, Chen MH, Salenius SA, et al. Mortality in men with localized prostate cancer treated with brachytherapy with or without neoadjuvant hormone therapy. Cancer. 2010 Feb 15;116(4):837-42. PMID: 20052734

Elliott SP, Meng MV, Elkin EP, et al. Incidence of urethral stricture after primary treatment for prostate cancer: data From CaPSURE. J Urol. 2007 Aug;178(2):529-34; discussion 534. PMID: 17570425

Fitzsimons NJ, Sun LL, Dahm P, et al. A single-institution comparison between radical perineal and radical retropubic prostatectomy on perioperative and pathological outcomes for obese men: an analysis of the Duke Prostate Center database. Urology. 2007 Dec;70(6):1146-51. PMID: 18158036

Forsythe K, Blacksburg S, Stone N, et al. Intensity-modulated radiotherapy causes fewer side effects than three-dimensional conformal radiotherapy when used in combination with brachytherapy for the treatment of prostate cancer. Int J Radiat Oncol Biol Phys. 2012 Jun 1;83(2):630-5. PMID: 22099032

Gacci M, Lapini A, Serni S, et al. Predictors of quality of life after radical treatment for prostate cancer. Urol Int. 2008;80(3):231-6. PMID: 18480622

Gillitzer R, Thomas C, Wiesner C, et al. Single center comparison of anastomotic strictures after radical perineal and radical retropubic prostatectomy. Urology. 2010 Aug;76(2):417-22. PMID: 19969328

Goldner G, Potter R, Battermann JJ, et al. Comparison between external beam radiotherapy (70 Gy/74 Gy) and permanent interstitial brachytherapy in 890 intermediate risk prostate cancer patients. Radiother Oncol. 2012 May;103(2):223-7. PMID: 22398311

Gonzalez-San Segundo C, Herranz-Amo F, Alvarez-Gonzalez A, et al. Radical prostatectomy versus external-beam radiotherapy for localized prostate cancer: long-term effect on biochemical control-in search of the optimal treatment. Ann Surg Oncol. 2011 Oct;18(10):2980-7. PMID: 21431406

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Appendix D. Risk of Bias Assessment for Key Question 1

Table 46. Risk-of-bias assessment for Key Question 1 (randomized controlled trials)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Wilt et al. 2012[16] Same study as Wilt et al. 2009[16] Prostate Intervention versus Observation Trial (PIVOT)	Overall mortality Prostate cancer–specific mortality Distant metastases Adverse events	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Medium

Table 46. Risk-of-bias assessment for Key Question 1 (randomized controlled trials) (continued)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Bill-Axelson et al. 2011[25] Same study as Johansson et al. 2011[47], Holmberg et al. 2012[54], and Bill-Axelson et al. 2008[46]	Overall mortality Prostate cancer–specific mortality Distant metastases Adverse events	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Low
Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	Quality of life (QOL)	Yes	Yes	Yes	Not reported	No	Yes	Yes	Yes	Medium

Table 46. Risk-of-bias assessment for Key Question 1 (randomized controlled trials) (continued)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Jones et al. 2011[26]	Overall survival Prostate cancer–specific mortality Biochemical failure Distant metastases Adverse events	Yes	Not reported	No	No	Yes	Yes	Yes	Yes	Medium
	QOL	Yes	Not reported	No	No	No	Yes	Yes	Yes	High
Giberti et al. 2009[21]	Biochemical disease-free survival Adverse events	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Medium
	QOL	Yes	Yes	Not reported	Yes	No	Yes	Yes	Yes	Medium

Table 46. Risk-of-bias assessment for Key Question 1 (randomized controlled trials) (continued)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Widmark et al. 2009[23]	Prostate cancer–specific mortality Biochemical failure Adverse events	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
D'Amico et al. 2008[24]	Overall mortality PCSM	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Martis et al. 2007[22]	Adverse events	Yes	Not reported	Not reported	Not reported	Yes	Yes	Yes	Yes	Medium

Table 47. Risk-of-bias assessment for Key Question 1 (nonrandomized comparative studies)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Resnick et al. 2013[44]	Quality of life (QOL) Urinary function QOL Bowel function QOL Sexual function	No	No	No	No	No	Yes	Yes	Yes	High
Abdollah et al. 2012[32]	Prostate cancer specific mortality	No	No	No	No	Yes	Yes	Yes	Yes	High
Barry et al. 2012[35]	Continence Sexual function	No	No	No	No	No	Yes	Yes	Yes	High
Kibel et al. 2012[31]	Overall survival Prostate cancer specific mortality	No	No	No	No	Yes	Yes	Yes	Yes	High
Mohammed et al. 2012[39]	Acute and late genitourinary and gastrointestinal toxicities	No	No	No	No	Yes	Yes	Yes	Yes	High
Rosenberg et al. 2012[33]	Prostate cancer specific mortality	No	No	No	No	Yes	Yes	Yes	Yes	High

Table 47. Risk-of-bias assessment for Key Question 1 (nonrandomized comparative studies) (continued)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Sheets et al. 2012[45]	Gastrointestinal morbidity Urinary incontinence Non-incontinence urinary morbidity Sexual dysfunction Hip fractures	No	No	No	No	Yes	Yes	Yes	Yes	High
Shen et al. 2012[42]	Prostate cancer specific mortality	No	No	No	No	Yes	Yes	Yes	Yes	High
Abdollah et al. 2011[49]	Prostate cancer specific mortality Other cause mortality	No	No	No	No	Yes	Yes	Yes	Yes	High
Bekelman et al. 2011[40]	Bowel complications Erectile complications Urinary complications	No	No	No	No	Yes	Yes	Yes	Yes	High
Williams et al. 2011[37]	Urinary complications Bowel complications Erectile dysfunction	No	No	No	No	Yes	Yes	Yes	Yes	High
Hadley et al. 2010[38]	All cause and prostate cancer specific mortality	No	No	No	No	Yes	Yes	Yes	Yes	High

Table 47. Risk-of-bias assessment for Key Question 1 (nonrandomized comparative studies) (continued)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Barocas et al. 2010[27]	Biochemical recurrence-free survival	No	No	No	No	Yes	Yes	Yes	Yes	High
Malcolm et al. 2009[34]	QOL urinary function QOL urinary bother QOL sexual function QOL sexual bother QOL bowel function QOL bowel bother	No	No	No	No	No	Yes	No	Yes	High
Dosoretz et al. 2010[41]	All-cause mortality	No	No	No	No	Yes	Yes	Yes	Yes	High
Krambeck et al. 2008[28]	Immediate (<1 month post-operative) and late (>1 month post-operative) QOL to determine complications Prostate cancer–specific mortality Other cause mortality Biochemical progression Systemic progression Clinical local recurrence	No	No	No	No	Yes	Yes	Yes	Yes	High

Table 47. Risk-of-bias assessment for Key Question 1 (nonrandomized comparative studies) (continued)

Study	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q5. Was the outcome measure of interest objective and was it objectively measured?	Q6. Was there a 15% or less difference in the length of followup for the two groups?	Q7. Did 85% or more of enrolled patients provide data at the time point of interest?	Q8. Was there fidelity to protocol?	Overall Risk of Bias Category
Lu-Yao et al. 2008[36]	Prostate cancer–specific survival and overall survival	No	No	No	No	Yes	Yes	Yes	Yes	High
Schroeck et al. 2008[29]	Prostate specific antigen recurrence rate	No	No	No	No	Yes	Yes	Yes	Yes	High
Albertsen et al. 2007[43]	Prostate cancer–specific survival Overall survival	No	No	No	No	Yes	Yes	Yes	Yes	High
Ferrer et al. 2008*[30]	QOL	No	No	No	No	No	Yes	Yes	Yes	High

Appendix E. Key Questions 1–4: Study Selection Criteria and Description of Treatment

Table 48. Description of study design and selection criteria and treatment (randomized controlled trials)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Wilt et al. 2012[16] Same study as Wilt et al. 2009[16] Prostate Intervention versus Observation Trial (PIVOT)	A multicenter randomized controlled trial (RCT) involving 731 men recruited from 52 medical centers (44 Veterans Affairs and 8 National Cancer Institute sites) across the USA. Enrollment Period: November 1994–January 2002	Eligible men had to have biopsy proven clinically localized prostate cancer (T1–T2NxM0) of any histologic grade, diagnosed within the past 12 months, prostatic specific antigen (PSA) value ≤50 ng/mL, age ≤75 years, bone scan negative for metastatic disease, an estimated life expectancy of at least 10 years and judged to be medically and surgically fit for radical prostatectomy.	Not reported.	Observation: Men were offered palliative (noncurative) therapy (e.g., transurethral resection of the prostate for local progression causing urinary obstruction, androgen deprivation and/or targeted radiation therapy for evidence of distant spread). Radical prostatectomy (RP): The technique used for radical prostatectomy (RP) was at the surgeon's discretion. Additional interventions were determined by each participant and his physician.

Table 48. Description of study design and selection criteria and treatment (randomized controlled trials) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Bill-Axelson et al. 2011[25] Same study as Johansson et al. 2011[47], Holmberg et al. 2012[54], and Bill-Axelson et al. 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	A multicenter RCT involving 695 men was conducted at 14 centers in Sweden, Finland, and Iceland. Enrollment Period: October 1989–December 1999	Men were eligible for inclusion if they were younger than 75 years of age and had a life expectancy of more than 10 years, had no other known cancers, and had a localized tumor T0d (later named T1b), T1, or T2. T1c patients were included in 1994. All patients included in the study were required to have a serum PSA <50ng/mL and a negative bone scan.	Not reported	Watchful Waiting: Men in the watchful waiting group who had signs of obstructive voiding disorders were treated with transurethral resection. Metastases detected by bone scan were managed with hormonal therapy. RP: The surgical procedure started with a lymphadenectomy of the obturator fossa; if no nodal metastases were found in frozen sections, the RP was performed. Radical excision of the tumor was given priority over nerve-sparing surgery.
Jones et al. 2011[26]	A multicenter phase 3 RCT involving 1,979 men was conducted in the USA and Canada. Enrollment Period: 1994–2001	Eligible men had to have histologically confirmed prostate cancer stage T1b, T1c, T2a, or T2b, and a PSA ≤20ng/mL. Other eligibility criteria included a Karnofsky performance score of 70 or more (on a scale of 1 to 100, with higher scores indicating better performance status), an alanine aminotransferase level that was no more than twice the upper limit of the normal range, no evidence of regional lymph node involvement or distant metastatic disease, and no previous chemotherapy, radiotherapy, hormonal therapy, cryosurgery, or definitive surgery for prostate cancer.	Not reported	External beam radiation therapy (EBRT): Radiotherapy was administered in daily 1.8 Gray (Gy) fractions prescribed to the isocenter of the treatment volume, consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate. EBRT plus short-term androgen deprivation therapy (ADT): Flutamide at a dose of 250 mg orally three times a day and either monthly subcutaneous goserelin at a dose of 3.6 mg or intramuscular leuprolide at a dose of 7.5 mg for 4 months. Radiotherapy commenced after 2 months of ADT.

Table 48. Description of study design and selection criteria and treatment (randomized controlled trials) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Giberti et al. 2009[21]	A single center RCT involving 200 men was conducted in Italy. Enrollment Period: May 1999–October 2002	Study included only Caucasian men with low risk prostate cancer (clinical stage T1c or T2a, PSA value ≤10 ng/mL and Gleason sum ≤6)	Previous pelvic irradiation, large median lobes, uroflow-Q max lower than 10 ml/s, history of multiple pelvic surgeries, previous transurethral resection of prostate, prostate volume greater than 60 mL and positive seminal vesicles biopsy.	Radical Retropubic prostatectomy (RRP): Bilateral nerve sparing RRP, in accordance with Walsh's principles, and standard lymph node dissection were performed on all the patients by a single surgeon. Brachytherapy: Brachytherapy was performed by a team, which included a urologist, a radiation therapist and a primary care physician, through a transperitoneal template-guided peripheral loading real-time technique and seeds of iIodine125. A D90 >140 Gy was considered the cut-off value in order to predict a good quality implant.

Table 48. Description of study design and selection criteria and treatment (randomized controlled trials) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Widmark et al. 2009[23]	A multicenter RCT involving 875 men was conducted at 47 centers in Norway, Sweden, and Denmark. Enrollment Period: February 1996–December 2002	*Study included men younger than 76 with a histologically-proven prostate cancer, who had a life expectancy of more than 10 years, and were categorized as clinical T1b–T2, G2–G3, or T3, any World health organization (WHO) Grade 1–3. Participants had a PSA ≤70 ng//mL and no evidence of metastases as determined by bone scanning and pulmonary radiography. ** This study reported separate data for T1b–T2 patients.*	Participants with nodal disease	ADT: LHRH-agonist, leuproline (Procren depot; 3.75 mg a months or 11.25 mg every 3 months), for 3 months and were simultaneously treated with 250 mg oral antiandrogen, flutamide three times a day. Flutamide was discontinued when antiandrogen treatment side effects occurred and then reinstituted with stepwise increased dose to at least 500 mg. If this failed, antiandrogen was changed to bicalutamide (150 mg once a day). ADT plus EBRT: ADT and a standard 3D conformal radiotherapy (3D-CRT) technique was applied with a prescribed central dose (of 50 Gy) to the prostate and seminal vesicles. A sequential boost of at least 20 Gy was added to the prostate, which received a total dose minimum of 70 Gy.

Table 48. Description of study design and selection criteria and treatment (randomized controlled trials) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
D'Amico et al. 2008[24]	A single center RCT involving 206 men was conducted in USA. Enrollment Period: December 1, 1995–April 15, 2001	Study included men with prostate cancer clinical stage T1b to T2bN0M0 who had at least a 10-year life expectancy excluding death from prostate cancer and an Eastern Cooperative Oncology Group performance status 0 to 1.	Patients with a history of a prior malignancy except for nonmelanoma skin cancer or prior pelvic radiation therapy or ADT.	EBRT: Daily dose of 1.8 Gy for initial 25 treatments, totaling 45 Gy, and 2.0 Gy for final 11 treatments, totaling 22 Gy. EBRT plus ADT: EBRT plus ADT which consisted of a luteinizing hormone-releasing agonist, leuprolide or goserelin and antiandrogen flutamide. Leuprolide was delivered intramuscularly each month at a dose 7.5 mg or 22.5 mg every 3 months. Goserelin was administered subcutaneously each month at a dose of 3.6 mg or 10.8 mg every 3 months. Flutamide was taken orally at a dose of 250 mg every 8 hours and starting 1 to 3 days before leuprolide.
Martis et al. 2007[22]	A single center RCT involving 200 men was conducted in Italy. Enrollment Date: January 1997–December 2004	Study included men with clinically localized prostate cancer (T1–T2).	For the perineal prostatectomy group, authors reported an exclusion of patients with a prostate weight >80 g, a prominent median lobe and inability to place the patient in an exaggerated lithotomy position because of hip arthrosis, ankylosis, and/or severe coxarthrosis.	Bilateral nerve sparing RP performed by the retropubic or perineal approach by a single surgeon.

Table 49. Description of study design and selection criteria and treatment (nonrandomized comparative studies)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Resnick et al. 2013[44]	This study was a secondary analysis of data from a subset of patients enrolled in the Prostate Cancer Outcomes Study (PCOS), a population-based cohort of men in whom prostate cancer had been diagnosed in the mid-1990s and who had been followed prospectively for 15 years. Enrollment Period: Patients were diagnosed in 1994 and 1995.	Men were enrolled in PCOS if they had prostate cancer. Patients were enrolled at six participating research centers throughout the United States. Patients under the age of 60 years, of Hispanic origin, and black men were over-sampled. For the current study, only those men with clinically localized prostate cancer diagnosed between the ages of 55 and 74 years, who had completed a 2-year or 5-year followup survey, and who underwent either prostatectomy or radiotherapy as primary treatment (with or without androgen-deprivation therapy) within one year after diagnosis were included.	NR	Prostatectomy Radiotherapy
Abdollah et al. 2012[32]	This was a population-based cohort study of men with localized, cT1 to T2 prostate cancer treated between 1992 and 2005. This study used the SEER registries-Medicare insurance program linked database. Enrollment Period: Patients were treated between 1992 and 2005.	Men ≥65 years diagnosed with nonmetastatic prostate cancer as their first malignant disease between 1992 and 2005. Patients had Medicare Part A and Part B claims available and were not enrolled in a health maintenance organization throughout the duration of the study.	Patients were excluded if their original or current reason for Medicare entitlement was listed as disability or had a Medicare status code including disability, their PC was diagnosed at autopsy or using the death certificate only, if they were treated surgically or with initial hormonal therapy, they had T3/T4 tumors, anaplastic or unknown grade, unknown stage, had missing socioeconomic data, or were >80 years at the time of diagnosis.	Radiotherapy Observation

Table 49. Description of study design and selection criteria and treatment (nonrandomized comparative studies) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Barry et al. 2012[35]	A population-based random sample was drawn from the 20% Medicare claims files for August 2008 through December 2008. Enrollment Period: November 2009–March 2010	Men with the following were included: had an inpatient claim for radical prostatectomy (ICD-9 SX code of 605 in any position); a prostate cancer diagnosis during the admission when the prostatectomy was performed (ICD-9 185, 1850, 2365, 2395, 2334, 19882, V1046, or V1045; a surgeon's claim for the procedure (CPT codes 55810, 55812, 55815, 55840, 55842, 55845, 55866, 55899, or 55899); ≥66 years of age at the time of surgery (to have 12 months of preoperative claims available); no health maintenance organization participation during 2008; and lived in the United States.	Patients who had died before selection or were residents of a nursing home were excluded.	Robotic-assisted Laparoscopic Radical Prostatectomy (RALRP) Open Retropubic Radical Prostatectomy (ORRP)

Table 49. Description of study design and selection criteria and treatment (nonrandomized comparative studies) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Kibel et al. 2012[31]	Data was gathered retrospectively on a cohort of 10,429 consecutive men with clinically localized prostate cancer treated between 1995 and 2005 at two sites in the United States. Enrollment Period: Patients were treated between 1995 and 2005.	NR	NR	Radical Prostatectomy (RP): The procedure was either retropubic or laparoscopic and the median cGy dose is not applicable. External Beam Radiation Treatment (EBRT): The procedure was 3DCRT, IMRT, or 4-field conventional EBRT. The median cGy dose 7800 (IQR 7,400 to 8,000) at site 1, 7,400 (7,070 to 7,544) at site 2. Brachytherapy: Brachytherapy was delivered using intraoperative treatment planning with ultrasound guidance. The median cGy dose 14,400 at site 1, 14,500 at site 2. In addition, 34% (N=1,348) patients treated with EBRT and brachytherapy also received neoadjuvant, concurrent and/or adjuvant androgen deprivation therapy (ADT).
Mohammed et al. 2012[39]	Cohort study of consecutive patients with clinical stage II to III adenocarcinoma of the prostate. Enrollment Period: Patients were treated between 1992 and 2006 at one U.S. site.	Men with clinical stage II to III adenocarcinoma of the prostate.	NR	BT with either high-dose or low-dose rate: Patients were clinical stage II. Image guided external beam radiotherapy (IG-EBRT) External beam radiotherapy with high-dose rate (HDR) BT boost (EBRT plus HDR): Patients were intermediate or high-risk disease.

Table 49. Description of study design and selection criteria and treatment (nonrandomized comparative studies) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Rosenberg et al. 2012[33]	Cohort study of men treated for intermediate risk adenocarcinorna of the prostate at one site in the United States. Enrollment Period: Patients were treated between 1997 and 2007.	Men were included in the study if they were treated with either brachytherapy plus EBRT or brachytherapy plus ADT; had an intermediate risk adenocarcinoma of the prostate; a Gleason score of ≤7 and PSA <20 ng/mL, or Gleason score of 7; or a Gleason score of 6 and PSA >10.	Men with low risk prostate cancer and those treated with brachytherapy alone were excluded.	Brachytherapy plus EBRT Brachytherapy plus ADT
Sheets et al. 2012[45]	This was a population-based study using Surveillance, Epidemiology, and End Results-(SEER) Medicare-linked data from 2000 to 20009 for patients with nonmetastatic prostate cancer. Enrollment Period: Patients received a diagnosis of prostate cancer between 2000 and 2007.	Men with a diagnosis of prostate cancer, no additional cancers, no metastatic disease, no disease diagnosis at autopsy, with the month and year of their prostate cancer diagnosis recorded, and at least one year of claims data before their diagnosis were included.	Men enrolled in a health maintenance organization within one year of diagnosis or not enrolled in Medicare Part A and Part B for the study duration were excluded. Patients who received combination therapy of radiation and either brachytherapy of prostatectomy were also excluded.	IMRT: 6,666 patients Conformal radiation therapy: 6,310 patients Proton therapy: 685 patients Just over 50% of IMRT and Conformal radiation patients and 31% OF Proton therapy patients had concurrent androgen deprivation therapy.
Shen et al. 2012[42]	Population based study of a cohort of patients with high-risk prostate cancer from the SEER database. Enrollment Period: Patients were diagnosed between 1998 and 2002.	Men who were diagnosed with T1 to T3N0MO prostate adenocarcinoma, received nonsurgical treatment with BT alone, BT plus EBRT, or EBRT alone, and had a Gleason score of 4 or 5 if only a single pattern was reported or a combined Gleason score of 8 to 10.	Patients with a surgery other than biopsy were excluded.	Brachytherapy Brachytherapy plus EBRT EBRT
Abdollah et al. 2011[49]	Population based cohort study using the SEER database. Enrollment Period: Patients were diagnosed between 1992 and 2005.	Men ≥65 years with nonmetastatic prostate cancer and both Part A and Part B Medicare claims available and not enrolled in a health maintenance organization were included.	Patients with prostate cancer diagnosed at autopsy or on death certificate only, or if their original or current reason for Medicare entitlement was listed as disability or a Medicare status code including disability were excluded.	RP Observation

Table 49. Description of study design and selection criteria and treatment (nonrandomized comparative studies) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Bekelman et al. 2011[40]	Observational cohort study based on the SEER database. Enrollment Period: Men were diagnosed between 2002 and 2004.	Men ≥65 years of age with non-metastatic prostate cancer diagnosed between 2002 and 2004 with followup through 2006 in the Medicare database.	NR	IMRT 3D-CRT
Williams et al. 2011[37]	A population-based study patients with localized prostate cancer using the SEER database. Enrollment Period: Men were diagnosed between 2001 and 2005.	Men ≥65 diagnosed with prostate cancer between 2001 and 2005. Prostate cancer was their only cancer diagnosis.	Men enrolled in health maintenance organizations, those not enrolled in <Medicare part A and B at diagnosis, patients undergoing combined therapy for prostate cancer or salvage cryotherapy, those with clinical stage T4 disease, distant metastasis or with insufficient followup, and those treated >9 months after diagnosis were excluded.	Cryotherapy Brachytherapy
Hadley et al. 2010[38]	Population based cohort study using the SEER database. Enrollment Period: Patients were diagnosed between 1995 and 2003.	Men aged 66–74 years with newly diagnosed and previously untreated prostate cancer and whose tumor state was T1 or T2	Patients with unusual histology, identified as having cancer through a death certificate or autopsy, not from a SEER registry, month of diagnosis or date of death unknown, aged 65 years and no data for previous year, incomplete Medicare Part A and Part B data because of managed care enrollment or only Part A enrollment for 1 year before or after diagnosis, distant stage or not clinical stage T1 or T2 disease, and treatment with chemotherapy, radiation therapy, or hormone therapy but without surgery.	RP: within 6 months of diagnosis from SEER surgery codes and International Classification of Diseases, Ninth Edition (ICD-9), and Current Procedural Terminology, Fourth Edition (CPT-4), codes from the Medicare claims. Conservative management: defined as no radiation, surgery, hormonal treatment, or chemotherapy within 6 months of diagnosis

Table 49. Description of study design and selection criteria and treatment (nonrandomized comparative studies) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Barocas et al. 2010[27]	Cohort study of patients undergoing RP for clinically localized prostate cancer at one institution in the United States. Enrollment Period: Patients were treated between June 2003 and January 2008.	Men undergoing RP for clinically localized prostate cancer.	Patients with prior hormonal therapy, radiation therapy, patients with positive lymph nodes, and those missing followup data were excluded.	RRP: RRP was performed in the anatomic fashion described by Walsh and Partin with modifications based on individual surgeon experience. RALP: RALP was performed by standard techniques with small modifications on 1 to 3 da Vinci surgical robots.
Dosoretz et al. 2010[41]	Retrospective review of medical records of men treated with brachytherapy for localized prostate cancer at 20 sites within the 21st Century Oncology Consortium. Enrollment Period: Patients received treatment from May 1991–September 2005. Followup ended January 2007.	Men with localized prostate cancer treated with ultrasound guided brachytherapy using iodine 125 or palladium 103 sources were enrolled.	Patients were excluded if they received supplemental external-beam radiation nor had <2 years of followup.	Brachytherapy using iodine 125 or palladium 103: 1,391 patients Brachytherapy using iodine 125 or palladium 103 plus ADT: 1,083 patients
Malcolm et al. 2009[34]	Cohort study of patients treated with open radical prostatectomy, robot assisted laparoscopic prostatectomy, brachytherapy, or cryotherapy. Patients completed a health-related QOL questionnaire before treatment and at 3, 6, 12, 18, 24, 30, and 36 months post-treatment. Enrollment Period: February 2000–December 2008	Men undergoing operative treatment for localized prostate cancer at one institution were invited to participate. Those who completed the baseline and at least one followup questionnaire were included.	Patients receiving multimodal treatments were excluded.	Open Radical Prostatectomy (ORP): retropubic or perineal route. Nerve sparing techniques were used where appropriate. Robot assisted laparoscopic prostatectomy (RALP): Nerve sparing techniques were used where appropriate. Brachytherapy: modified peripheral loading low dose rate technique was used with permanent palladium seeds delivering an average dose of 125 Gy. Cryotherapy: Third generation cryotherapy delivery system.

Table 49. Description of study design and selection criteria and treatment (nonrandomized comparative studies) (continued)

Study	Design and Study Enrollment Period	Patient Inclusion Criteria	Patient Exclusion Criteria	Treatment
Krambeck et al. 2008[28]	Retrospective matched comparison study of men with prostatic adenocarcinoma treated with RRP or RARP. Enrollment Period: August 2002–December 2005	Men with clinically localized prostate cancer treated between August 2002 and December 2005 at one institution in the United States were enrolled.	NR	RRP RARP
Lu-Yao et al. 2008[36]	Population-based cohort study of men ≥66 receiving Medicare who did not receive definitive local therapy for clinical stage t1 to T2 prostate cancer using the SEER database. Enrollment Period: Patients were diagnosed between 1992 and 2002.	Men ≥66 years of age who were SEER residents and diagnosed with T1 to T2 cancer in 1992 to 2002.	Men who died or received definitive local therapy within 180 days of diagnosis and those without both Medicare Part A and Part B as their primary healthcare insurance coverage during the study period were excluded. Patients with missing data, unknown cancer, or initiation of ADT before the cancer diagnosis were also excluded.	Primary androgen deprivation therapy (PADT) Conservative management: These patients did not have surgery, radiation or PADT.
Schroeck et al. 2008[29]	Cohort study of men with clinically localized prostate cancer treated at one site in the United States. Enrollment Period: Patients were treaded between August 2003 and January 2007.	Consecutive men with clinically localized prostate cancer treated between August 2003 and January 2007 with either RRP or RALP.	Patients who had a RALP converted to an open procedure were excluded.	RRP RALP: Procedure was done using the Vattikuti institute technique and the three-arm da Vinci surgical system.
Albertsen et al. 2007[43]	Retrospective, population based study using data from the Connecticut Tumor Registry. Enrollment Period: Patients were diagnosed with prostate cancer from 1990 to 1992.	Men diagnosed in a community setting with localized prostate cancer, treated with surgery, radiation, or observation, residing in Connecticut, with age at diagnosis ≤75 years.	Males with advanced prostate cancer or an initial PSA ≥50 ng/mL were excluded.	Surgery EBRT Observation
Ferrer et al. 2007[30]	Longitudinal prospective study of consecutive men with clinically localized prostate cancer. Enrollment Period: April 2003 through March 2005 at 10 sites in Spain.	Men with clinically localized prostate cancer, stages T1 or T2 and no previous transurethral prostate resection were enrolled.	NR	RP 3D-CRT Brachytherapy

Appendix F. Baseline Demographic and Tumor Characteristics

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Wilt et al. 2012[16] Same study as Wilt et al. 2009[16] Prostate Intervention versus Observation Trial (PIVOT)	Observation: 367 patients	Mean 66.8±5.6 years Age ≥65 years: 64.3%	Black: 33% White: 60% Other: 7.1	Myocardial infarction [MI] (11.7) Congestive heart failure [CHF] (2.2) Peripheral vascular disease [PVD] (5.5) Cerebral vascular disease [CVD] (4.4) Stroke (4.9) Diabetes (16.1) Chronic obstructive pulmonary disease [COPD] (6.8)	Prostatic specific antigen [PSA] (ng/mL; mean [SD]): 10.2 (7.9), Median: 7.7 Clinical stage (% of patients): 1A: 3.0 1B: 2.5 1C: 49.9 2A: 23.2 2B: 12.0 2C: 9.0 Gleason grade (% of patients): Grade 2–4: 21.5 Grade 5–6: 53.1 Grade 7: 18.9 Grade 8–10: 5.6 Mean Gleason grade (SD): 5.5 (1.6) Histologic grade (% of patients): Well differentiated: 24.2 Moderately well differentiated: 64.2 Poorly differentiated: 6.1 Unknown: 5.5 Tumor risk category (based on PSA, Gleason grade and tumor stage) [% of patients]: Low: 44.0 Medium: 34.9 High: 21.1

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Wilt et al. 2012[16] Same study as Wilt et al. 2009[16] Prostate Intervention versus Observation Trial (PIVOT) (continued)	Radical Prostatectomy (RP): 364 patients	Mean: 67.0±5.2 years Age ≥65 years: 66.5%	Black: 30.5% White: 63.7% Other: 5.9%	MI (10.2) CHF (0.8) PVD (4.1) CVD (1.9) Stroke (3.9) Diabetes (15.4) COPD (10.2)	PSA (ng/mL; mean [SD]): 10.1 (7.4), Median 7.9 Clinical stage (% of patients): 1A: 1.1 1B: 1.4 1C: 50.8 2A: 26.4 2B: 12.9 2C: 6.6 Gleason grade (% of patients): Grade 2–4: 22.9 Grade 5–6: 48.7 Grade 7: 21.5 Grade 8–10: 6.7 Mean Gleason grade (SD): 5.6 (1.5) Histologic grade (% of patients): Well differentiated: 25.1 Moderately well differentiated: 60.5 Poorly differentiated: 8.0 Unknown: 6.4 Tumor risk category (based on PSA, Gleason grade and tumor stage) [% of patients: Low: 42.6 Medium: 37.2 High: 20.2

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Bill-Axelson et al. 2011[25] Same study as Johansson et al. 2011[47], Holmberg et al. 2012[54], and Bill-Axelson et al. 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	RP: 347 patients	Mean: 64.6±5.1 years Age <65 years: 60±3.5 Age ≥65 years: 68.4±2.5	Not reported	Not reported	Mean PSA, ng/Ml: 13.5 Tumor stage, No (%): T1b: 33 (9.5) T1c: 43 (12.4) T2: 270 (77.8) Unknown: 1 (0.3) WHO grade, No (%): Grade 1: 168 (48.4) Grade 2: 178: (51.3) Unknown: 1 (0.3) Gleason score, at biopsy, No (%): Score 2-4: 45 (13.0) Score 5-6: 165 (47.6) Score 7: 77 (22.2) Score 8-10: 14 (4.0) Unknown: 46 (13.3) PSA level, No (%): Level <4 mg/mL: 43 (12.4) Level 4-6.9 ng/mL: 60 (17.3) Level 7-10: 68 (19.6) Level 10.1-20: 100 (28.8) Level ≥20: 69 (19.9) Unknown: 7 (2.0) Positive margins in RPS, No (%): Margin 0 mm: 184 (64.8) Margin 1-9 mm: 50 (17.6) Margin 10-19 mm: 25 (8.8) Margin ≥20 mm: 24 (8.5) Missing data: 1 (0.4) Extracapsular extension in radical prostatectomy specimen [RPS], No (%): Extension 0 mm: 151 (53.2) Extension 1-9 mm: 46 (16.2) Extension 10-19 mm: 38 (13.4) Extension ≥20 mm: 48 (16.9) Missing data: 1 (0.4) Gleason score of RPS, No (%): Score 2-6: 88 (31.0) Score 7; 3+4: 87 (30.6) Score 7; 4+3: 70 (24.6) Score 8-10: 38 (13.4) Missing data: 1 (0.4)

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Bill-Axelson et al. 2011[25] Same study as Johansson et al. 2011[47], Holmberg et al. 2012[54], and Bill-Axelson et al. 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial (continued)	Watchful waiting: 348 patients	Mean: 64.5±5.0 years Age <65 years: 60.2±3.4 Age ≥65 years: 68.4±2.4	Not reported	Not reported	Mean PSA, ng/Ml: 12.3 Tumor stage, No (%): T1b: 50 (14.4) T1c: 38 (10.9) T2: 259 (74.4) Unknown: 1 (0.3) WHO grade, No (%): Grade 1: 166 (47.7) Grade 2: 182 (52.3) Unknown: 0 (0.0) Gleason score, at biopsy, No (%): Score 2-4: 46 (13.2) Score 5–6: 166 (47.7) Score 7: 82 (23.6) Score 8–10: 21 (6.0) Unknown: 33 (9.5) PSA level, No (%): Level <4 mg/mL: 63 (18.1) Level 4–6.9 ng/mL: 60 (17.2) Level 7–10: 67 (19.3) Level 10.1–20: 95 (27.3) Level ≥20: 60 (17.2) Unknown: 3 (0.9)

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Jones et al., 2011[26]	External beam radiotherapy (EBRT): 992 patients	Median: 71 years (range: 47–88)	White: 756 (76) Black: 197 (20) Hispanic: 26 (3) Other or unknown: 13 (1)	Present: 712 (72) Absent: 275 (28) Unknown: 5 (<1)	PSA [number (%)]: Level <4 ng/mL: 100 (10) Level 4–20 ng/mL: 892 (90) Tumor stage [number (%)]: T1: 476 (48) T2: 516 (52) Nodal stage [number (%)]: NX: 954 (96) N0: 38 (4) Gleason score [number (%)]: Score 2–6: 592 (60) Score 7: 286 (29) Score 8–10: 87 (9) Unknown: 27 (3) Differentiation [number (%)]: Well differentiated: 150 (15) Moderately differentiated: 620 (62) Poorly differentiated or undifferentiated: 222 (22) Risk subgroup [number (%)]: Low risk: 334 (34) Intermediate risk: 544 (55) High risk: 114 (11)

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Jones et al., 2011[26] (continued)	EBRT plus Androgen Deprivation Therapy (ADT): 987 patients	Median: 70 years (range: 47–91)	White: 745 (75) Black: 198 (20) Hispanic: 27 (3) Other or unknown: 17 (2)	Present: 742 (75) Absent: 245 (25) Unknown: 5 (<1)	PSA [number (%)]: Level <4 ng/mL: 109 (11) Level 4–20 ng/mL: 878 (89) Tumor stage [number (%)]: T1: 488 (49) T2: 499 (51) Nodal stage [number (%)]: NX: 944 (96) N0: 43 (4) Gleason score [number (%)]: Score 2–6: 623 (63) Score 7: 252 (26) Score 8-10: 93 (9) Unknown: 19 (2) Differentiation [number (%)]: Well differentiated: 135 (14) Moderately differentiated: 625 (63) Poorly differentiated or undifferentiated: 227 (23) Risk subgroup [number (%)]: Low risk: 351 (36) Intermediate risk: 524 (53) High risk: 112 (11)

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Giberti et al., 2009[21]	Radical retropubic prostatectomy: 100 patients	Mean: 65.2 years (range: 57–74)	Caucasian: 100 (100)	Not reported	Mean PSA (ng/mL): 7.8 (3.5–10) Mean Gleason score: 5.9 Prostate volume (mL): 43.9 (19–56) Tumor stage: T1c patients: 64 T2a patients: 36
	Brachytherapy: 100 patients	Mean: 65.6 years (range: 56–74)	Caucasian: 100 (100)	Not reported	Mean PSA (ng/mL): 7.5 (2.9–9.3) Mean Gleason score: 5.7 Prostate volume (mL): 41.7 (21–60) Tumor stage: T1c patients: 59 T2a patients: 41

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Widmark et al., 2009[23]	ADT: 439 patients	Mean: 66.2±5.1 years	Not reported	Not reported	Mean PSA (ng/mL): 19.8 Tumor stage, number (%): T1b: 1 (0.2) T1c: 7 (1.6) T2: 83 (18.9) T3: 347 (79) Unknown: 1 (0.2) Seminal vesicle involvement, number (%): 107 (24.4) PSA, number (%): Level <4 ng/mL: 26 (5.9) Level 4–10 ng/mL: 104 (23.7) Level 10.1–20 ng/mL: 132 (30.1) Level 20.1–30 ng/mL: 90 (20.5) Level >30 ng/mL: 87 (19.8)
	ADT plus EBRT: 436 patients	Mean: 65.7±5.5 years	Not reported	Not reported	Mean PSA (ng/mL): 19.9 Tumor stage, number (%): T1b: 2 (0.5) T1c: 9 (2.1) T2: 86 (19.7) T3: 335 (76.8) Unknown: 4 (0.9) Seminal vesicle involvement, number (%): 96 (22.0) PSA, number (%): Level <4 ng/mL: 22 (5.0) Level 4–10 ng/mL: 110 (25.2) Level 10.1–20 ng/mL: 132 (30.3) Level 20.1–30 ng/mL: 85 (19.5) Level >30 ng/mL: 87 (20.0)

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
D'Amico et al., 2008[24]	EBRT: 104 patients	None or minimal comorbidity: 78 patients	Median: 73 (Range: 51–81) ≤60: 4 (5%) >60 75 (95%)	**Adult Comorbidity Evaluation (ACE)-27 comorbidity score** Score 0 (none): 68 (86) Score 1 (minimal): 11 (14) Score 2 (Moderate): not applicable Score 3 (Severe): not applicable	PSA, median (Range), ng/mL: 11.2 (3.1–40.0) Gleason score, [number (%)]: Score 5–6: 21 (27) Score 7: 50 (63) Score 8–10: 8 (10) Tumor category, [number (%)]: T1b: 1 (1) T1c: 33 (42) T2a: 20 (25) T2b: 25 (32)
		Moderate or severe comorbidity: 25 patients	Median: 74 (Range: 61–81) ≤60: 0 (0%) >60: 25 (100%)	**ACE-27 comorbidity score** Score 0 (none): not applicable Score 1 (minimal): not applicable Score 2 (Moderate): 22 (88) Score 3 (Severe): 3 (12)	PSA, median (Range), ng/mL: 10.8 (0.9–24.8) Gleason score, [number (%)]: Score 5–6: 6 (24) Score 7: 11 (44) Score 8–10: 8 (32) Tumor category, [number (%)]: T1b: 1 (4) T1c: 8 (32) T2a: 6 (24) T2b: 10 (40)

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
D'Amico et al., 2008[24] (continued)	EBRT plus ADT: 102 patients	None or minimal comorbidity: 78 patients	Median: 72 (Range: 49–82) ≤60: 2 (3%) >60: 76 (97%)	**ACE-27 comorbidity score** Score 0 (None): 67 (86) Score 1 (Minimal): 11 (14) Score 2 (Moderate): not applicable Score 3 (Severe): not applicable	PSA, median (Range), ng/mL: 11.5 (3.1–36.0) Gleason score, [number (%)]: Score 5–6: 26 (33) Score 7: 42 (54) Score 8–10: 10 (13) Tumor category, [number (%)]: T1b: 1 (1) T1c: 46 (59) T2a: 13 (17) T2b: 18 (23)
		Moderate or severe comorbidity: 24 patients	Median: 72 (Range: 61–79) ≤60: 0 (0%) >60: 24 (100%)	**ACE-27 comorbidity score** Score 0 (none): not applicable Score 1 (minimal): not applicable Score 2 (Moderate): 21 (88) Score 3 (Severe): 3 (12)	PSA, median (Range), ng/mL: 10.0 (1.3 – 21.1) Gleason score, [number (%)]: Score 5–6: 4 (17) Score 7: 16 (67) Score 8–10: 4 (17) Tumor category, [number (%)]: T1b: 1 (4) T1c: 8 (33) T2a: 7 (29) T2b: 8 (33)

Table 50. Baseline demographic and tumor characteristics (randomized controlled trials) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Martis et al., 2007[22]	Radical Perineal Prostatectomy: 100 patients	64.2±6.5 years	Not reported	Not reported	Mean PSA (ng/mL): 7.9 (3.5–11.6) Mean Gleason score: 5.5 (4–7) Clinical stage [number (%)]: T1a: 20 (20) T2a: 60 (60) T2b: 20 (20)
	Radical Retropubic Prostatectomy: 100 patients	65.4±7.2 years	Not reported	Not reported	Mean PSA (ng/mL): 9.2 (4.7–12.3) Mean Gleason score: 5.5 (4–7) Clinical stage [number (%)]: T1a: 24 (24) T2a: 58 (58) T2b: 18 (18)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Resnick et al. 2013[44]	Prostatectomy: 1,164 patients	Median (interquartile range [IQR]): 64 years (59–68)	Non-Hispanic White: 806 (75.9%) Non-Hispanic Black: 170 (11.7%) Hispanic: 188 (12.4%)	Coexisting illnesses: n (%) 0: 513 (42.5) 1: 368 (33.7) 2: 179 (15.2) ≥3: 104 (8.4) Note: self-reported pre-operative health data was gathered post-surgery.	Gleason score n (%): 2–4: 743 (63.9) 5–7: 216 (18.2) 8–10: 73 (6.5) Unknown: 132 (11.4) Prostate-specific antigen n (%): <4.0 ng/mL: 122 (9.8) 4.0–10.0 ng/mL: 703 (61.0) >10.0 ng/mL: 339 (29.2)
	Radiotherapy: 491 patients	Median (IQR): 69 years (64–71)	Non-Hispanic White: 370 (82.0%) Non-Hispanic Black: 65 (10.4%) Hispanic: 56 (7.7%)	Coexisting illnesses: n (%) 0: 159 (33.3) 1: 160 (33.1) 2: 93 (16.9) ≥3: 79 (16.7) Note: Self-reported pre-operative health data was gathered post-surgery.	Gleason score n (%): 2–4: 292 (59.3) 5–7: 110 (22.1) 8–10: 46 (9.6) Unknown: 43 (8.9) Prostate-specific antigen n (%): <4.0 ng/mL: 43 (9.4) 4.0–10.0 ng/mL: 252 (55.9) >10.0 ng/mL: 196 (34.7)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Abdollah et al. 2012[32]	Radiotherapy: 46,521 patients	Age n (%) 65–69 years: 11,209 (24.1%) 70–74 years: 19,279 (41.4%) 75–80 years: 16,033 (34.5%)	Race n (%) White: 40,437 (86.9%) Black: 3,716 (8.0%) Other: 2,368 (5.1%)	Charleston comorbidity index (%) 0: 20,100 (43.2%) 1: 13,835 (29.7%) ≥2: 12,586 (27.1%)	Clinical stage n (%): T1: 18,946 (40.7%) T2a/b: 22,127 (47.6%) T2c: 5,448 (11.7%) Gleason score n (%): <6: 2,555 (5.5%) 6–7: 31,544 (67.8%) 8–10: 12,422 (26.7%)
	Observation: 22,276 patients	Age n (%) 65–69 years: 4,866 (21.8%) 70–74 years: 7,563 (34.0%) 75–80 years: 9,847 (44.2%)	Race n (%) White: 18,355 (82.3%) Black: 2,440 (11.0%) Other: 1,501 (6.7%)	Charleston comorbidity index (%): 0: 9,584 (43.0%) 1: 5,832 (26.2%) ≥2: 6,860 (30.8%)	Clinical stage n (%) T1: 11,542 (51.8%) T2a/b: 9,222 (41.4%) T2c: 1,512 (6.8%) Gleason score n (%) <6: 3,906 (17.5%) 6–7: 15,067 (67.6%) 8–10: 3,303 (14.8%)
Barry et al. 2012[35]	Robotic-assisted laparoscopic radical prostatectomy (RALRP): 406 patients	66–69 years: 41.1%; 70–74 years: 43.8%; ≥75 years: 15.0%	Non-Hispanic White: 90.5% African American: 4.2% Hispanic: 2.5% Other: 2.7%	Comorbid illness: NR Self-rated overall health poor, fair, or good: 27.9% Self-rated overall health very good: 44.7% Self-rated overall health excellent: 27.4% Note: Self-reported pre-operative health data was gathered post-surgery.	NR
	Open retropubic radical prostatectomy (ORRP): 220 patients	66–69 years: 38.2%; 70–74 years: 46.4%; ≥75 years: 15.5%	Non-Hispanic White: 91.7% African American: 3.2% Hispanic: 2.3% Other: 2.8%	Comorbid illness: NR Self-rated overall health poor, fair, or good: 34.1% Self-rated overall health very good: 45.8% Self-rated overall health excellent: 20.1% Note: Self-reported pre-operative health data was gathered post-surgery.	NR

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Mohammed et al. 2012[39]	Brachytherapy (BT): 417 patients (high-dose rate [HDR]=210, low-dose rate [LDR]=207)	Mean age: 64.9 years (range: 40–83) years	NR	NR	Clinical stage: T1a–T1c: 273 (65%) T2a–T2c: 144 (35%) T3–T4: 0 (0%) Gleason score: 4–6: 371 (89%) 7: 42 (10%) 8–10: 3 (1%) PSA: ≤4: 98 (24%) 4.1–10.0: 301 (72%) >10.0: 18 (4%) Mean % Cores+: 23% Perineural invasion: 3% Mean prostate gland volume: 36.6%
	Image-Guided Radiation Therapy (EB-IGRT): 1,039 patients	Mean age: 70.8 years (range: 45–88) years	NR	NR	Clinical stage: T1a–T1c: 689 (67%) T2a–T2c: 321 (31%) T3–T4: 16 (2%) Gleason score: 4–6: 544 (53%) 7: 377 (36%) 8–10: 110 (11%) PSA ≤4: 155 (15%) 4.1–10.0: 661 (64%) >10.0: 218 (21%) Mean % Cores+: 35% Perineural invasion: 10% Mean prostate gland volume: 50.6%

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Mohammed et al. 2012[39] (continued)	EBRT plus HDR: 447 patients	Mean age: 67.1 years (range: 42–85) years	NR	NR	Clinical stage: T1a–T1c: 107 (24%) T2a–T2c: 282 (64%) T3–T4: 54 (12%) Gleason score: 4–6: 163 (36%) 7: 190 (43%) 8–10: 92 (21%) PSA: ≤4: 27 (6%) 4.1–10.0: 228 (52%) >10.0: 187 (42%) Mean % Cores+: 51% Perineural invasion: 25% Mean prostate gland volume: 41.9%

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Rosenberg et al. 2012[33]	BT plus EBRT: 186 patients	Median (IQR): 67.8 years (61.2–71.3)	NR	NR	Median (IQR) PSA ng/mL 8.51 (6.5–12.1) AJCC T-category n (%) T1b: 0 (0%) T1c: 78 (41.9%) T2a: 70 (37.6%) T2b: 38 (20.4%) Gleason score n (%) ≤6: 24 (12.9%) 3+4: 97 (52.1%) 4+3: 65 (34.9%)
	BT plus Androgen Deprivation Therapy (ADT): 621 patients	Median (IQR): 72.5 years (68.2–76.3)	NR	NR	Median (IQR) PSA ng/mL 10.3 (6.7–13.0) AJCC T-category n (%) T1b: 3 (0.5%) T1c: 425 (68.4%) T2a: 143 (23%) T2b: 50 (8%) Gleason score n (%) ≤6: 254 (40.9%) 3+4: 252 (40.5%) 4+3: 115 (18.5%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Sheets et al. 2012[45]	Intensity-modulated radiation therapy (IMRT): 6,666 patients	Age at diagnosis: 66 to 69 years: 1,338 (20.1%) 70 to 74 years: 2,415 (36.2%) ≥75 years: 2,913 (43.7)	White: 5,694 (85.4%) Black: 521 (7.8%) Other/unknown: 451 (6.8%)	Diabetes: 1,750 (26.2) Anticoagulation, arrhythmias, or valvular disease: 1,685 (25.3%) Gastrointestinal diagnosis/procedure: 1,359 (20.4%) Urinary nonincontinence diagnosis/procedure: 1,453 (21.8%) Urinary incontinence diagnosis/procedure: 1,475 (22.1%) Erectile dysfunction diagnosis/procedure: 615 (9.2%) Hip fracture: 20 (0.3%)	Tumor grade well/moderately differentiated: 3,390 (50.9%) Poorly differentiated: 3,177 (47.7%) Unknown/not assessed: 99 (1.5%) Clinical stage: T1: 3,375 (50.6%) T2: 3,070 (46.1%) T3/T4: 221 (3.3%)
	Three-dimensional conformal radiation therapy (3D-CRT): 6,310 patients	Age at diagnosis 66 to 69 years: 1,265 (20.1%) 70 to 74 years: 2,345 (37.2%) ≥75 years: 2,700 (42.8)	White: 5,325 (84.4%) Black: 657 (10.4%) Other/unknown: 328 (5.2%)	Diabetes: 1,681 (26.6) Anticoagulation, arrhythmias, or valvular disease: 1,533 (24.3%) Gastrointestinal diagnosis/procedure: 1,238 (19.6%) Urinary nonincontinence diagnosis/procedure: 1,331 (21.1%) Urinary incontinence diagnosis/procedure: 1,032 (16.3%) Erectile dysfunction diagnosis/procedure: 501 (7.9%) Hip fracture: 14 (0.2%)	Tumor grade well/moderately differentiated: 3,850 (61.0%) Poorly differentiated: 2,334 (37.0%) Unknown/not assessed: 126 (2.0%) Clinical stage T1: 2,502 (39.7%) T2: 3,556 (56.3%) T3/T4: 252 (4.0%)
	Proton Beam Therapy: 685 patients	Age at diagnosis 66–69 years: 248 (36.2%) 70–74 years: 233 (34.0%) ≥75 years: 204 (29.8%)	White: 634 (92.6%) Black: 20 (2.9%) Other/unknown: 31 (4.5%)	Diabetes: 130 (19.0%) Anticoagulation, arrhythmias, or valvular disease: 144 (21.0%) Gastrointestinal diagnosis/procedure: 148 (21.6%) Urinary nonincontinence diagnosis/procedure: 104 (15.2%) Urinary incontinence diagnosis/procedure: 109 (15.9%) Erectile dysfunction diagnosis/procedure: 83 (12.1%) Hip fracture: 0 (0%)	Tumor grade well/moderately differentiated: 413 (60.3%) Poorly differentiated: 268 (39.1%) Unknown/not assessed: 4 (0.6%) Clinical stage: T1: 348 (50.8%) T2: 314 (45.8%) T3/T4: 23 (3.4%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Shen et al. 2012[42]	BT: 910 patients	Median age: 70 years	White: 83.8% Black: 9.4% Asian: 6.3% Other: 0.5% Hispanic: 95.8% Non-Hispanic: 4.2%	Only prostate cancer: 78.7% Prostate first primary: 11.9% Prostate second or later: 9.5%	Post-1998 PSA elevated at diagnosis: 75.5% PSA borderline: 7.0% PSA normal at diagnosis: 3.5% PSA unknown/other: 14.1% Clinical stage T1: 37.4% T2: 59.2% T3: 3.4%
	BT plus EBRT: 2,466 patients	Median age: 70 years	White: 79.1% Black: 13.1% Asian: 6.9% Other: 0.9% Hispanic: 94.2% Non-Hispanic: 7.4%	Only prostate cancer: 78.8% Prostate first primary: 13.5% Prostate second or later: 7.6%	Post-1998 PSA elevated at diagnosis: 79.0% PSA borderline: 5.6% PSA normal at diagnosis: 4.7% PSA unknown/other:10.6% Clinical stage T1: 26.0% T2: 68.6% T3: 5.4%
	EBRT: 9,369 patients	Median age: 72 years	White: 77.7% Black: 11.3% Asian: 10.0% Other: 1.0% Hispanic: 93.9% Non-Hispanic: 6.1%	Only prostate cancer: 76.9% Prostate first primary: 14.5% Prostate second or later: 8.6%	Post-1998 PSA elevated at diagnosis: 81.8% PSA borderline: 4.6% PSA normal at diagnosis: 3.6% PSA unknown/other:10.0% Clinical stage T1: 22.4% T2: 66.8% T3: 10.8%

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Kibel et al. 2012[31]	Radical prostatectomy (RP): 6,485 patients, 2,843 at site 1 and 3,642 at site 2	Median (IQR) at site 1 (Cleveland Clinic): 60 years (56 to 65) Median (IQR) at site 2 (Barnes-Jewish Hospital): 61 years (55 to 66)	N (%) African American at site 1 (Cleveland Clinic): 310 (11%). N (%) African American at site 2 (Barnes-Jewish Hospital): 334 (9%).	Site 1 (Cleveland Clinic) Comorbidity index n (%): None: 2307 (81%) Mild: 377 (13%) Moderate: 150 (5%) Severe: 9 (0.3%). Site 2 (Barnes-Jewish Hospital) Comorbidity index n (%): None: 2,157 (59%) Mild: 1213 (33%) Moderate: 237 (7%) Severe: 35 (1%) Note comorbid illness data was prospectively recorded using medical records and the Adult Comorbidity Evaluation 27 index at site 1 while comorbidity was recorded through retrospective review of medical records using the Charleston Comorbidity Index at site 2.	Site 1 (Cleveland Clinic) Median ng/mL PSA (IQR): 5.9 (4.6 to 8.2) Site 2 (Barnes-Jewish Hospital) Median ng/mL PSA (IQR): 5.4 (4.1 to 7.8) Site 1 (Cleveland Clinic) bGS n (%): 2 to 6: 1,980 (70%) 7: 745 (26%) 8 to 10: 118 (4%) Site 2 (Barnes-Jewish Hospital) bGS n (%): 2 to 6: 2,774 (76%) 7: 710 (20%) 8 to 10: 158 (4%) Site 1 (Cleveland Clinic) clinical stage n (%): T1ab: 15 (0.5%) T1c: 2,074 (73%) T2a: 554 (20%) T2b: 124 (4%) T2c: 48 (2%) T3: 28 (1%) Site 2 (Barnes-Jewish Hospital) clinical stage n (%): T1ab: 40 (1%) T1c: 2,921 (80%) T2a: 364 (10%) T2b: 250 (7%) T2c: 49 (1%) T3: 18 (0.5%) Site 1 (Cleveland Clinic) D'Amico risk group n (%): low: 1,669 (59%) Intermediate: 945 (33%) High: 229 (8%) Site 2 (Barnes-Jewish Hospital) D'Amico risk group n (%): Low: 2,297 (63%) Intermediate: 1,049 (29%) High: 296 (8%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Kibel et al. 2012[31] (continued)	EBRT: 2,264 patients, 1,638 at site 1 and 626 at site 2	Median (IQR) at site 1 (Cleveland Clinic): 69 years (63 to 73) Median (IQR) at site 2 (Barnes-Jewish Hospital): 70 years (65 to 75)	N (%) African American at site 1 (Cleveland Clinic): 434 (27%). N (%) African American at site 2 (Barnes-Jewish Hospital): 101 (16%).	Site 1 (Cleveland Clinic) Comorbidity index n (%): None: 1084 (66%) Mild: 317 (19%) Moderate: 241 (12%) Severe: 39 (3%). Site 2 (Barnes-Jewish Hospital) Comorbidity index n (%): None: 220 (35%) Mild: 277 (44%) Moderate: 107 (17%) Severe: 22 (3%) Note comorbid illness data was prospectively recorded using medical records and the Adult Comorbidity Evaluation 27 index at site 1 while comorbidity was recorded through retrospective review of medical records using the Charleston Comorbidity Index at site 2.	Site 1 (Cleveland Clinic) Median ng/mL PSA (IQR): 8.9 (6.0 to 15.9) Site 2 (Barnes-Jewish Hospital) Median ng/mL PSA (IQR): 6.8 (4.7 to 10.7) Site 1 (Cleveland Clinic) bGS n (%): 2 to 6: 789 (47%) 7: 606 (37%) 8 to 10: 243 (16%) Site 2 (Barnes-Jewish Hospital) bGS n (%): 2 to 6: 390 (61%) 7: 172 (29%) 8 to 10: 64 (10%) Site 1 (Cleveland Clinic) clinical stage n (%): T1ab: 25 (2%) T1c: 883 (54%) T2a: 351 (22%) T2b: 158 (10%) T2c: 92 (6%) T3: 129 (8%) Site 2 (Barnes-Jewish Hospital) clinical stage n (%): T1ab: 7 (1%) T1c: 396 (62%) T2a: 112 (19%) T2b: 54 (9%) T2c: 20 (3%) T3: 37 (6%) Site 1 (Cleveland Clinic) D'Amico risk group n (%): Low: 479 (29%) Intermediate: 619 (37%) High: 540 (34%) Site 2 (Barnes-Jewish Hospital) D'Amico risk group n (%): Low: 283 (44%) Intermediate: 207 (35%) High: 136 (21%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Kibel et al. 2012[31] (continued)	BT: 1,680 patients, 1,330 at site 1 and 350 at site 2	Median (IQR) at site 1 (Cleveland Clinic): 68 years (62 to 72) Median (IQR) at site 2 (Barnes-Jewish Hospital): 69 years (63 to 73)	N (%) African American at site 1 (Cleveland Clinic): 149 (11%). N (%) African American at site 2 (Barnes-Jewish Hospital): 31 (9%).	Site 1 (Cleveland Clinic) Comorbidity index n (%): None: 809 (61%) Mild: 322 (24%) Moderate: 179 (14%) Severe: 20 (1%). Site 2 (Barnes-Jewish Hospital) Comorbidity index n (%): None: 163 (47%) Mild: 123 (35%) Moderate: 56 (16%) Severe: 8 (2%) Note comorbid illness data was prospectively recorded using medical records and the Adult Comorbidity Evaluation 27 index at site 1 while comorbidity was recorded through retrospective review of medical records using the Charleston Comorbidity Index at site 2.	Site 1 (Cleveland Clinic) Median ng/mL PSA (IQR): 6.1 (4.8 to 8.0) Site 2 (Barnes-Jewish Hospital) Median ng/mL PSA (IQR): 5.2 (3.8 to 6.8) Site 1 (Cleveland Clinic) bGS n (%): 2 to 6: 1,080 (81%) 7: 247 (18%) 8 to 10: 13 (1%) Site 2 (Barnes-Jewish Hospital) bGS n (%): 2 to 6: 313 (89%) 7: 36 (10%) 8 to 10: 1 (1%) Site 1 (Cleveland Clinic) clinical stage n (%): T1ab: 7 (0.5%) T1c: 1036 (83%) T2a: 211 (16%) T2b: 9 (1%) T2c: 7 (0.5%) T3: 0 (0%) Site 2 (Barnes-Jewish Hospital) clinical stage n (%): T1ab: 0 (0%) T1c: 265 (76%) T2a: 66 (19%) T2b: 17 (5%) T2c: 2 (1%) T3: 0 (0%) Site 1 (Cleveland Clinic) D'Amico risk group n (%): Low: 932 (70%) Intermediate: 370 (28%) High: 28 (2%) Site 2 (Barnes-Jewish Hospital) D'Amico risk group n (%): Low: 272 (78%) Intermediate: 73 (21%) High: 5 (1%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Abdollah et al. 2011[49]	RP: 22,244 patients	Mean age: 69.8 years (range: 65–80)	White: 19,926 (89.6%) Black: 1,334 (6.0%) Other: 984 (4.4%)	Charlson comorbidity index: 0: 11,249 (50.6%) 1: 6,582 (29.6%) 2: 2,712 (12.2%) ≥3: 1,701 (7.6%)	Clinical stage: T1: 7,448 (33.5%) T2a/b: 11,322 (50.9%) T2c: 3,474 (15.6%) Gleason score: 2–5: 1,089 (4.9%) 6–7: 15,173 (68.2%) 8–10: 5,982 (26.9%)
	Observation: 22,450 patients	Mean age: 73.5 years (range: 65–80)	White: 18,463 (82.2%) Black: 2,466 (11.0%) Other: 1,521 (6.8%)	Charlson comorbidity index: 0: 9,642 (42.9%) 1: 5,882 (26.2%) 2: 3,344 (14.9%) ≥3: 3,582 (16.0%)	Clinical stage: T1: 11,629 (51.8%) T2a/b: 9,293 (41.4%) T2c: 1,528 (6.8%) Gleason score: 2–5: 3,941 (17.6%) 6–7: 15,181 (67.6%) 8–10: 3,328 (14.8%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Bekelman et al. 2011[40]	IMRT: 5,845 patients	Age at diagnosis: 65–74 years: 3,204 (55%) ≥75 years: 2,641 (45%)	White: 4,851 (83%) Black: 521 (9%) Other: 371 (6%) Unknown: 102 (2%) Non-Hispanic: 5,384 (92%) Hispanic: 311 (5%) Unknown: 150 (3%)	Comorbidity index: 0: 1,470 (25%) 1: 1,759 (30%) ≥2: 2,616 (45%)	American Joint Committee on cancer (AJCC) tumor stage: T1: 2,511 (43%) T2: 3,081 (51%) T3: 215 (4%) T4: 38 (1%) Gleason score: 8–10: 1,590 (27%) 5–7: 4,091 (70%) 2–4: 61 (1%) Unknown: 103 (2%) History of transurethral resection of the prostate (TURP): 228 (4%)
	3D-CRT: 6,753 patients	Age at diagnosis: 65–74 years: 3,684 (55%) ≥75 years: 3,069 (45%)	White: 5,707 (85%) Black: 708 (10%) Other: 249 (4%) Unknown: 89 (1%) Non-Hispanic: 6,207 (92%) Hispanic: 384 (6%) Unknown: 162 (2%)	Comorbidity index: 0: 1,669 (24%) 1: 2,065 (31%) ≥2: 3,019 (45%)	AJCC tumor stage: T1: 2,547 (38%) T2: 3,908 (58%) T3: 230 (3%) T4: 68 (1%) Gleason score: 8–10: 1,937 (29%) 5–7: 4,603 (68%) 2–4: 107 (2%) Unknown: 106 (2%) History of TURP: 321 (5%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Williams et al. 2011[37]	BT: 9,985 patients	65–69 years: 3,233 (32.4%) 70–74 years: 3,643 (36.5%) ≥75: 3,109 (31.1%)	White: 8,496 (85.1%) Black: 624 (6.3%) Hispanic: 374 (3.8%) Asian: 302 (3.0%) Other/unknown: 189 (1.9%)	Charlson comorbidity score: 0: 7,534 (75.5%) 1: 1732 (17.4%) ≥2: 563 (5.6%) Unknown: 156 (1.6%) Incontinence diagnosis: 213 (2.1%) ED diagnosis: 967 (9.7%)	Clinical stage: T1: 4,956 (49.6%) T2: 4811 (48.2%) T3/unknown: 218 (2.2%) Tumor grade: Well/moderately differentiated: 8,433 (84.5%) Poorly differentiated: 1,291 (12.9%) Unknown/missing: 261 (2.6%) PSA: Elevated: 7,051 (70.6%) Normal: 817 (8.2%) Unknown: 2,117 (21.2%) Prior TURP: 208 (2.1%)
	Cryotherapy: 943 patients	65 to 69 years: 218 (23.1%) 70 to 74 years: 366 (35.6%) ≥75: 389 (41.3%)	White: 722 (76.6%) Black: 113 (12.0%) Hispanic: 47 (5.0%) Asian: 31 (3.3%) Other/unknown: 30 (3.2%)	Charlson comorbidity score: 0: 666 (70.6%) 1: 201 (21.3%) ≥2: 65 (6.9%) Unknown: 11 (1.2%) Incontinence diagnosis: 34 (3.6%) ED diagnosis: 103 (10.9%)	Clinical stage: T1: 369 (39.1%) T2: 530 (56.2%) T3/unknown: 44 (4.7%) Tumor grade: Well/moderately differentiated: 571 (60.6%) Poorly differentiated: 338 (35.8%) Unknown/missing: 34 (3.6%) PSA: Elevated: 641 (68.0%) Normal: 65 (6.9%) Unknown: 237 (25.1%) Prior TURP: 49 (5.2%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Hadley et al. 2010[38]	Conservative management : 5,879 patients	Unweighted sample: 66–69: 44.1% 70–74: 55.9%	Unweighted sample: White non-Hispanic: 70.0% White Hispanic: 6.3% African American: 16.%9 All other: 6.8%	Unweighted sample: NCI comorbidity index: 0: 75.4% 1: 10.0% ≥2: 9.3% Unknown: 5.4%	Unweighted sample: Stage: T1: 61.0% T2: 39.0% Grade: Well differentiated: 9.6% Moderately differentiated: 69.6% Poorly differentiated: 14.0% Unknown: 6.9%
	RP: 11,936 patients	Unweighted sample: 66–69: 53.2% 70–74: 46.8%	White non-Hispanic: 80.7% White Hispanic: 6.9% African American: 7.8% All other: 4.6%	Unweighted sample: NCI comorbidity index: 0: 57.8% 1: 8.4% ≥2: 8.9% Unknown: 23.4%	Unweighted sample: Stage: T1:64.9% T2:35.1% Grade: Well differentiated: 7.1% Moderately differentiated:70.8% Poorly differentiated: 21.0% Unknown: 1.1%

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Barocas et al. 2010[27]	RRP: 491 patients	Mean age: 62 years (7.3)	N (%) Nonwhite: 47 (9.6%)	NR	Median PSA: 5.8 ng/mL (IQR 4.6 to 8.4) N clinically palpable 144 (29.5%) Biopsy Gleason score ≤6: 327 (66.6%) 7: 116 (23.6%) 8 to 10: 48 (9.8%) Pathological stage pT0: 3 (0.6%) pT2: 342 (69.6%) pT3: 144 (29.3%) pT4: 2 (0.4%) Extraprostatic extension: 133 (27.1%) Positive seminal vesicles: 38 (7.7%) SM+: 148 (30.1%) Pathological Gleason Score: ≤6: 221 (45.3%) 7: 213 (43.6%) 8 to 10: 54 (11.1%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Barocas et al. 2010[27] (continued)	Radical retropubic prostatectomy (RALP): 1,413 patients	Mean age: 61 years (7.3)	N (%) Nonwhite: 92 (6.5%)	NR	Median PSA: 5.4 ng/mL (IQR 4.3 to 7.4) N clinically palpable: 315 (22.4%) Biopsy Gleason score: ≤6: 986 (69.9%) 7: 353 (25.0%) 8 to 10: 72 (5.1%) Pathological stage: pT0: 7 (0.5%) pT2: 1,136 (80.5%) pT3: 268 (19.0%) pT4: 0 (0%) Extraprostatic extension: 253 (17.9%) Positive seminal vesicles: 55 (3.9%) SM+: 281 (19.9%) Pathological Gleason Score: ≤6: 723 (51.5%) 7: 588 (41.8%) 8 to 10: 94 (6.7%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Dosoretz et al. 2010[41]	BT: 1,391 patients	Median age was 73 years for all patients enrolled.	NR	NR	For patients <73 years: Median PSA 5.9 Gleason score: ≤6: 641(90%) 7: 60 (8%) 8–10: 10 (1%) AJCC tumor classification: T1: 496 (70%) T2: 215 (30%) T3: NA D'Amico risk group: Low: 539 (76%) Intermediate: 111 (16%) High: 61 (9%) For patients ≥73 years: Median PSA 6.7 Gleason score: ≤6: 586 (86%) 7: 77 (11%) 8–10: 17 (3%) AJCC tumor classification: T1: 394 (58%) T2: 285 (42%) T3: 1 (0.2%) D'Amico risk group: Low: 428 (63%) Intermediate: 143 (21%) High: 109 (16%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Dosoretz et al. 2010[41] (continued)	BT plus ADT: 1,083 patients		NR	NR	For patients <73 years: Median PSA 6.2 Gleason score: ≤6: 426 (86%) 7: 54 (11%) 8–10: 15 (3%) AJCC tumor classification: T1: 319 (64%) T2: 176 (36%) T3: NA D'Amico risk group: Low: 323 (65%) Intermediate: 120 (24%) High: 52 (11%) For patients ≥73 years: Median PSA 7.6 Gleason score: ≤6: 461 (78%) 7: 104 (18%) 8–10: 23 (4%) AJCC tumor classification: T1: 393 (67%) T2: 190 (32%) T3: 5 (1%) D'Amico risk group: Low: 320 (54%) Intermediate: 193 (33%) High: 75 (13%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Malcolm et al. 2009[34]	Open Radical Prostatectomy (ORP): 135 patients	Mean: 59±7 years	N (%) White: 102 (76%) Black: 32 (24%) Other: 1 (1%)	NR	No (%) clinical stage: T1c or less: 112 (83%) T2a: 17 (13%) T2b+: 6 (4%) Unknown: 0 (0%) N (%) Gleason score: ≤6: 93 (69%) 7: 34 (25%) ≥8: 8 (6%) Median (IQR) PSA: 5.7 ng/mL (4.7 to 7.3)
	Robotic-assisted laparoscopic prostatectomy (RAP): 447 patients	Mean: 59±6 years	N (%) White: 341 (76%) Black: 78 (17%) Other: 28 (6%)	NR	No (%) clinical stage: T1c or less: 340 (76%) T2a: 68 (15%) T2b+: 32 (7%) Unknown: 7 (2%) N (%) Gleason score: ≤6: 269 (60%) 7: 154 (34%) ≥8: 24 (5%) Median (IQR) PSA: 5.2 ng/mL (3.9 to 6.8)
	BT: 122 patients	Mean: 66±7 years	N (%) White: 89 (73%) Black: 29 (24%) Other: 4 (3%)	NR	No (%) clinical stage: T1c or less: 98 (80%) T2a: 16 (13%) T2b+: 3 (2%) Unknown: 5 (4%) N (%) Gleason score: ≤6: 88 (72%) 7: 28 (23%) ≥8: 6 (5%) Median (IQR) PSA: 6.0 ng/mL (4.5 to 8.2)
	Cryotherapy: 81 patients	Mean: 71±7 years	N (%) White: 60 (74%) Black: 19 (23%) Other: 2 (2%)	NR	No (%) clinical stage: T1c or less: 57 (70%) T2a: 10 (12%) T2b+: 13 (16%) Unknown: 1 (1%) N (%) Gleason score: ≤6: 40 (50%) 7: 34 (41%) ≥8: 7 (9%) Median (IQR) PSA: 6.2 ng/mL (5.0 to 8.6)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Krambeck et al. 2008[28]	RRP: 588 patients	Median age at surgery: 61 years (range, 41 to 77)	NR	NR	Median PSA level: 5.0 (range 0.6 to 39.7) Clinical stage: T1a/b: 4 (0.7%) T1c: 418 (71.1%) T2a: 130 (22.1%) T2b: 28 (4.8%) T3 or T4: 8 (1.4%) Biopsy Gleason grade: <6: 0 (0%) 6: 441 (75.0%) 7: 133 (22.6%) ≥8: 14 (2.3%) Pathological stage: T2aN0: 206 (35.0%) T2bN0: 315 (53.6%) T3aN0: 35 (6.0%) T3b4N0: 24 (4.1%) TxN+: 8 (1.4%) Pathological Gleason grade: 6: 391 (66.5%) 7: 167 (28.4%) ≥8: 30 (5.1%)
	Robotic-assisted radical prostatectomy (RARP): 294 patients	Median age at surgery: 61 years (38 to 76)	NR	NR	Median PSA level: 4.9 (range 0.5 to 33.5) Clinical stage: T1a/b: 0 (0%) T1c: 214 (72.8%) T2a: 75 (25.5%) T2b: 4 (1.4%) T3 or T4: 1 (0.3%) Biopsy Gleason grade: <6: 2 (0.7%) 6: 212 (72.1%) 7: 70 (23.8%) ≥8: 10 (3.4%) Pathological stage: T2aN0: 105 (35.8%) T2bN0: 159 (54.3%) T3aN0: 15 (5.1%) T3b4N0: 14 (4.8%) TxN+: 0 (0%) Pathological Gleason grade: 6: 192 (65.5%) 7: 87 (29.7%) ≥8: 14 (4.8%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Lu-Yao et al. 2008[36]	Primary androgen deprivation therapy (PADT): 7,867 patients	Median (IQR): 79 years (74 to 83)	Black: 758 (9.6%)	Charlson Comorbidity status: 0 to 1: 7,446 (94.7%) ≥2: 421 (5.3%)	Cancer grade: Well-differentiated: 64 (0.8%) Moderately differentiated: 5,115 (65.0%) Poorly differentiated: 2,688 (34.2%) Clinical stage: T1: 3,915 (49.8%) T2: 3,952 (50.2%)
	Conservative management: 11,404 patients	Median (IQR): 77 years (72 to 81)	Black: 1,307 (11.5%)	Charlson Comorbidity status: 0 to 1: 10,664 (93.5%) ≥2: 740 (6.5%)	Cancer grade: Well-differentiated: 244 (2.1%) Moderately differentiated: 9,545 (83.7%) Poorly differentiated: 1,615 (14.2%) Clinical stage: T1: 7,325 (64.2%) T2: 4,079 (35.8%)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Schroeck et al. 2008[29]	RRP: 435 patients	Median (IQR): 60.3 years (55.3 to 64.7)	African American: 74 (17.1%) Other: 359 (82.9%)	NR	Median PSA (IQR): 5.3 (4.1 to 7.2) Clinical stage: T1: 296 (72.4%) T2: 101 (24.7%) T3: 12 (2.9%) Biopsy Gleason score: 2 to 6: 241 (58.8%)\ 7: 127 (31.0%) 8 to 10: 42 (10.2%) D'Amico risk classification: Low: 189 (50.9%) Intermediate: 125 (33.7%) High: 57 (15.4%) Median EBL (IQR): 800 (500 to 1200) Lymphadenectomy: 313 (72.0%) Pathological stage: T2: 324 (74.5%) ≥T3: 111 (25.5%) Pathological Gleason score: 2 to 6: 177 (40.7%) 7: 199 (45.7%) 8 to 10: 59 (13.6%) Pathological node status: pN0: 225 (96.6%) pN1: 8 (3.4%) Seminal vesicle invasion: 42 (9.7%) Extracapsular extension: 102 (23.4%) PSM status: 122 (28.0%) Median (IQR) Prostate weight in grams: 41.3 (32.4 to 52.0)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Schroeck et al. 2008[29] (continued)	RALP: 362 patients	Median (IQR): 59.2 years (54.5 to 63.8)	African American: 56 (16.6%) Other: 282 (83.4%)	NR	Median PSA (IQR): 5.4 (4.1 to 7.1) Clinical stage: T1: 281 (83.1%) T2: 57 (16.9%) T3: 0 (0%) Biopsy Gleason score: 2 to 6: 254 (72.2%)\ 7: 89 (25.3%) 8 to 10: 9 (2.6%) D'Amico risk classification: Low: 211 (65.7%) Intermediate: 95 (29.6%) High: 15 (4.7%) Median EBL (IQR): 150 (100 to 173) Lymphadenectomy: 271 (74.9%) Pathological stage T2: 287 (79.3%) ≥T3: 75 (20.7%) Pathological Gleason score: 2 to 6: 168 (46.4%) 7: 176 (48.6%) 8 to 10: 18 (5.0%) Pathological node status: pN0: 163 (99.4%) pN1: 1 (0.6%) Seminal vesicle invasion: 11 (3.0%) Extracapsular extension: 71 (19.6%) PSM status 106 (29.3%) Median (IQR) Prostate weight in grams: 42.9 (34.3 to 55.0)

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Albertsen et al. 2007[43]	Surgery: 596 patients	Median: 65 years	NR	% Charlson comorbidity score >1: 4%	% DRE finding: 1 nodule: 34% Multiple nodules on one side: 3% Nodule 2 sides: 2% % Gleason score: 2 to 4: 3% 5: 5% 6: 53% 7: 27% 8 to 10: 12% % PSA (ng/mL): 0 to 3.9: 11% 4 to 9.9: 46% 10 to 19: 28% 20 to 49: 15% Median: 9.1 % D'Amico risk category: Low: 35% Intermediate: 39% High: 26%

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Albertsen et al. 2007[43] (continued)	Radiation: 642 patients	Median: 71 years	NR	% Charlson comorbidity score >1: 10%	% DRE finding: 1 nodule: 32% Multiple nodules on one side: 6% Nodule 2 sides: 4% % Gleason score: 2 to 4: 3% 5: 6% 6: 46% 7: 25% 8 to 10: 20% % PSA (ng/mL): 0 to 3.9: 9% 4 to 9.9: 40% 10 to 19: 29% 20 to 49: 22% Median: 10.3 % D'Amico risk category Low: 26% Intermediate: 36% High: 38%

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Albertsen et al. 2007[43] (continued)	Observation: 114 patients	Median: 70 years	NR	% Charlson comorbidity score >1: 11%	% DRE: Multiple nodules on one side: 4% Nodule 2 sides: 0% % Gleason score: 2 to 4: 17% 5: 15% 6: 46% 7: 11% 8 to 10: 11% % PSA (ng/mL): 0 to 3.9: 27% 4 to 9.9: 44% 10 to 19: 17% 20 to 49: 12% Median: 6.6 % D'Amico risk category Low: 58% Intermediate: 20% High: 22%

Table 51. Baseline demographic and tumor characteristics (nonrandomized comparative studies) (continued)

Study	Intervention/ Number of Patients	Age	Race	Comorbid Illness (%)	Tumor Characteristics
Ferrer et al. 2007[30]	RP: 134 patients	Mean age: 64±5.5 years	NR	NR	Mean PSA: 7.9 (3.3) Mean Gleason score: 6.8 (6.2) Clinical stage: T1: 88 (65.7) T2: 46 (34.3) Tx: 0 (0) Risk group: Low: 58 (43.3) Intermediate: 71 (53.0) High: 5 (3.7)
	3D-CRT: 205 patients	Mean: 69.2±5.5 years	NR	NR	Mean PSA: 10.1 (7.9) Mean Gleason score: 6.0 (1.1) Clinical stage: T1: 106 (51.7) T2: 95 (46.3) Tx: 4 (2.0) Risk group: Low: 98 (47.8) Intermediate: 70 (34.1) High: 37 (18.0)
	BT: 275 patients	Mean: 66.9±6.5 years	NR	NR	Mean PSA: 6.9 (2.3) Mean Gleason score: 5.7 (4.4) Clinical stage: T1: 224 (81.5) T2: 51 (18.5) Tx: 0 (0) Risk group: Low: 241 (87.6) Intermediate: 32 (11.6) High: 2 (0.7)

Appendix G. Evidence Tables

Table 52. Overall mortality (randomized controlled trials)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Wilt et al. 2012[16] Prostate Intervention versus Observation Trial (PIVOT)	Observation: 364 patients	Radical Prostatectomy [RP]: 364 patients	Hazard ratio [HR] (95% confidence interval [CI], p–value for interaction
Overall death from any cause at median followup of 10 years (number of events/total number of patients)	183/367	171/364	0.88 (0.71–1.08)
Age			p=0.85
<65 years	50/131	43/122	0.89 (0.59–1.34)
>65 years	133/236	128/242	0.84 (0.63–1.08)
Race			p=0.81
White	119/220	117/232	0.84 (0.65–1.08)
Black	53/121	46/111	0.93 (0.62–1.38)
Other	11/26	8/21	0.85 (0.34–2.11)
Charlson score			p=0.79
0	86/220	82/224	0.90 (0.66–1.23)
≥1	97/157	89/140	0.84 (0.63–1.13)
Performance score			p=0.66
0	146/310	139/312	0.89 (0.71–1.13)
1–4	37/57	32/52	0.82 (0.51–1.31)
Prostate specific antigen (PSA)			p=0.04
≤10	101/241	110/238	1.03 (0.79–1.35)
>10	77/125	61/126	0.67 (0.48–0.94)
Risk			p=0.07
Low	54/148	62/148	1.15 (0.80–1.66)
Intermediate	70/120	59/129	0.69 (0.49–0.98)
High	49/80	42/77	0.74 (0.49–1.13)
Gleason score			p=0.87
<7	125/261	113/254	0.86 (0.67–1.12)
≥7	47/86	50/98	0.84 (0.56–1.25)

Table 52. Overall mortality (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Bill-Axelson et al. 2011[25] Same study as Holmberg et al. 2012[54], and Bill-Axelson et al. 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	Watchful waiting: 348 patients	RP: 347 patients	Absolute Risk Reduction (ARR) and or Relative Risk (RR), 95% CI, p-value for interaction
Total number of deaths, cumulative incidence (number (% [95% CI]) at a median followup of 10.8 years (range, 3 weeks to 17.2 years)	156 (44.8)	137 (39.5)	p=0.09
All ages at 8 years followup	22.4 (18.4–27.3)	17.9 (14.3–22.4)	ARR with RP, % (95% CI): 4.6 (-1.4–10.5)
All ages at 12 years followup	39.8 (34.7–45.7)	32.7 (27.9–38.4)	ARR with RP: 7.1 (-0.5–14.7) RR with RP: 0.82 (0.65–1.03) p=0.09
Age <65 years at 8 years followup	23.5 (17.8–30.9)	12.1 (7.9–18.5)	ARR with RP: 11.4 (3.1–19.6)
Age <65 years at 12 years followup	40.2 (33.0 – 49.0)	21.9 (16.1–29.9)	ARR with RP: 18.3 (7.8–28.8) RR with RP: 0.59 (0.41–0.85) p=0.004
Age ≥65 years at 8 years followup	21.4 (16.2–28.3)	22.6 (17.4–29.5)	ARR with RP: -1.2 (-9.6–7.30)
Age ≥65 years at 12 years followup	39.3 (32.5–47.7)	42 (35–50.5)	ARR with RP: -2.7 (-13.5–8.0) RR with RP: 1.04 (0.77–1.40) p=0.81
Total number of deaths, cumulative incidence (number (% [95% CI]) at 15 years followup	201 (57.8)	166 (47.8)	p=0.007
All at 15 years followup	52.7 (40.8–52.0)	6.6 (-1.3–14.5)	ARR with RP: 46.1 (40.8–52.0) RR with RP: 0.75 (0.61–0.92) p=0.007
Low risk cancer at 15 years followup	44.6 (36.6–54.4)	31.4 (23.9–41.3)	ARR with RP: 13.2 (0.9–25.5) RR with RP: 0.62 (0.42–0.92) p=0.02
Age <65 years at 15 years followup	47.4 (40.0–56.1)	33.9 (26.9–42.6)	ARR with RP: 13.2 (0.9–25.5) RR with RP: 0.52 (0.37–0.73) p<0.001
Age <65 years and low risk cancer at 15 years followup	36.2 (26.1–50.2)	16.9 (9.5–30.1)	ARR with RP: 19.3 (4.0–34.7) RR with RP: 00.36 (0.18–0.70) p=0.002

Table 52. Overall mortality (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Age ≥65 years at 15 years followup	57.4 (50.2–65.8)	56.7 (49.5–65.0)	ARR with RP: 0.7 (-10.3–11.7) RR with RP: 0.98 (0.75–1.28) p=0.89
Age ≥65 years and low risk cancer at 15 years followup	52.9 (41.3–67.6)	46.8 (35.1–62.3)	ARR with RP: 6.1 (-12.6–24.8) RR with RP: 0.92 (0.57–1.49) p=0.74
D'Amico et al. 2008[24]	External Beam Radiation Therapy (EBRT): 104 patients	EBRT plus Androgen Deprivation Therapy (ADT): 102 patients	HR, 95% CI, p-value for interaction
Overall death in all patients at median followup of 7.6 years (range 0.5–11.0)	44	30	1.8 (1.1– -2.9), p=0.01
Overall death (No or Minimal Comorbidity)	31	11	4.2 (2.1–8.5), p<0.001
Overall death (Moderate or Severe Comorbidity)	13	19	0.54 (0.27–1.10), p=0.08
D'Amico et al. 2008[24]	Radiation therapy: 103 patients	Radiation therapy plus AST: 98 patients	HR (95% CI)
Overall mortality at a median of 4.52 years followup	23	12	2.07 (1.02–4.20), p=0.04

Table 53. Overall mortality (nonrandomized comparative studies)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Dosoretz et al. 2010[41]	Brachytherapy: 1,391 patients	Brachytherapy with ADT: 1,083 patients	Cox regression analysis of time to all-cause mortality. Hazard ratio (95% CI) for adjusted risk of all-cause mortality by patient baseline characteristics.
All-cause mortality – all patients	NA	NA	Cox regression analysis time to all-cause mortality: There was a significant interaction between hormone therapy and increasing age (adjusted HR 1.04 (1.01 to 1.07), p=0.0035). Age and hormone therapy use (p=0.0049) were also significantly associated with risk of ACM whereas known prostate cancer prognostic risk factors, including PSA, biopsy Gleason score, clinical T classification were not associated.
All-cause mortality – all patients	NA	NA	Adjusted HR for age: 1.03 (1.01 to 1.05), p=0.0013
All-cause mortality – all patients	NA	NA	Adjusted HR for PSA: 1.003 (0.996 to 1.010), p=0.4252
All-cause mortality – all patients	NA	NA	Adjusted HR for Gleason score: <7 reference, ≥7 1.186 (0.972 to 1.448), p=0.0937
All-cause mortality – all patients	NA	NA	Adjusted HR for tumor classification: T1 reference, T2 or T3 0.977 (0.831 to 1.149), p=0.7816
All-cause mortality – all patients	NA	NA	Adjusted HR for ADT no reference, ADT=yes 0.049 (0.0006 to 0.403), p=0.0049
All-cause mortality – all patients	NA	NA	Adjusted HR for ADT*age: 1.043 (1.014 to 1.072), p=0.0035
All-cause mortality – <73 years	NA	NA	Adjusted HR for age: 1.03 (0.996 to 1.055), p=0.084
All-cause mortality – <73 years	NA	NA	Adjusted HR for PSA: 1.123 (0.896 to 1.406), p=0.3132
All-cause mortality – <73 years	NA	NA	Adjusted HR for Gleason score: <7 reference, ≥7 0.916 (0.616 to 1.363), p=0.665
All-cause mortality - <73 years	NA	NA	Adjusted HR for tumor classification: T1 reference, T2 or T3 0.904 (0.685 to 1.194), p=0.4769
All-cause mortality – <73 years	NA	NA	Adjusted HR for ADT no reference, ADT=yes 0.874 (0.662 to 1.153), p=0.3402
All-cause mortality – ≥73 years	NA	NA	Adjusted HR for age: 1.055 (1.025 to 1.085), p=0.0022
All-cause mortality – ≥73 years	NA	NA	Adjusted HR for PSA: 1.015 (0.876 to 1.176), p=0.8451
All-cause mortality – ≥73 years	NA	NA	Adjusted HR for Gleason score: <7 reference, ≥7 1.293 (1.026 to 1.630), p=0.0297
All-cause mortality – ≥73 years	NA	NA	Adjusted HR for tumor classification: T1 reference, T2 or T3 1.014 (0.829 to 1.240), p=0.8945
All-cause mortality – ≥73 years	NA	NA	Adjusted HR for ADT no reference, ADT=yes 1.243 (1.013 to 1.1525), p=0.0369

Table 53. Overall mortality (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Hadley et al. 2010[38]	Conservative management: 5,879 patients	Radical Prostatectomy (RP): 11,936 patients	Cox proportional hazards model using three approaches: traditional multivariable survival analysis, propensity score adjustment, and instrumental variable analysis
Multivariable survival analysis	0.249 (0.237 to 0.263)	0.177 (0.170 to 0.185)	HR 1.47 (1.35 to 1.59)
Propensity score adjustments (inverse probability of treatment weights [IPTW])	0.236 (0.223 to 0.248)	0.185 (0.177 to 0.193	HR 1.54 (1.46 to 1.62)
Propensity score adjustments (standardized mortality ratio weights [SMRW])	0.250 (0.237 to 0.263)	0.203 (0.195 to 0.211)	HR 1.46 (1.33 to 1.59)
Instrumental variable approach	0.208 (0.199 to 0.218)	0.192 (0.183 to 0.201)	HR 1.09 (0.46 to 2.59)
Krambeck et al. 2008[28] Death from any cause	Radical Retropubic Prostatectomy (RRP): 4 patients	Robotic-Assisted Radical Prostatectomy (RARP): 4 patients	Median followup time was 1.3 years.
Lu-Yao et al. 2008[36] overall mortality – all cancer grades combined	Primary Androgen Deprivation Therapy (PADT): 4,729/39,767 events/person-year, rate per 100=11.9	Conservative management 6,316/66,567 events/person-year, rate per 100=9.5	Adjusted HR (95% CI) 1.17 (1.12 to 1.21) p<0.05

Table 54. Overall survival (randomized controlled trials)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Jones et al. 2011[26]	External Beam Radiation Therapy (EBRT): 992 patients	EBRT plus Androgen Deprivation Therapy (ADT): 987 patients	Hazard Ratio [HR] (95% confidence interval [CI])
Overall survival at 10 years [number of patients (% reaching end point)]			
All patients	992 (57)		1.17 (1.01–1.35), p=0.03
Low risk	334 (64)		1.07 (0.83–1.39)
Intermediate risk	544 (54)		1.23 (1.02–1.49), p=0.03
High risk	114 (51)		1.16 (0.78–1.71)
White	756 (57)		1.19 (1.01–1.41), p=0.04
Black	197 (55)		1.15 (0.84–1.58)
Age ≤70 years	471 (64)		1.23 (0.98–1.54)
Age >70 years	521 (50)		1.11 (0.92–1.33)
D'Amico et al. 2008[24]	EBRT: 104 patients	EBRT plus ADT: 102 patients	
Kaplan-Meir estimates of 5-year survival rates, % points (95% CI)	78% (68%–88%)	88% (80%–95%)	
Rates of survival free of salvage AST at 5 years, % points (95% CI)	57% (46%–69%)	82% (73%–90%)	
D'Amico et al. 2008[24]	EBRT: 103 patients	EBRT plus ADT: 98 patients	HR (95% CI)
Survival free of salvage AST at median of 4.52 years followup, number of patients	43	21	2.30 (1.36–3.89), p=0.002

Table 55. Overall survival (nonrandomized comparative studies)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Kibel et al. 2012[31] Adjusted 10-year overall survival	Radical Prostatectomy (RP): 88.9% (95% CI, 87.5 to 90.1)	External Beam Radiation Therapy (EBRT): 82.6% (95% CI, 79.8 to 85.0)	Brachytherapy (BT): 81.7% (95% CI, 78.7 to 84.4)	Kaplan-Meier analysis p-value NR.
Overall survival multivariable analysis (treatment group)	1.0 (referent)	1.6 (95% CI, 1.4 to 1.9)	1.7 (95% CI, 1.4 to 2.1)	Hazard ratio (HR) p-value: <0.001
Overall survival multivariable analysis (patient age)	NA	NA	NA	HR 2.2 (95% CI, 1.7–2.9), p<0.001.
Overall survival multivariable analysis (African-American ethnicity)	NA	NA	NA	HR 1.5 (95% CI, 1.2–1.8), p<0.001.
Overall survival multivariable analysis (comorbidity)	NA	NA	NA	HR none=1.0 (referent); mild 1.6 (1.4–1.8), moderate 3.3 (2.8–3.9), severe 5.0 (3.6–7.0), p<0.001.
Overall survival multivariable analysis (pretreatment PSA)	NA	NA	NA	HR 1.5 (95% CI, 1.3 to 1.7), p<0.001.
Overall survival multivariable analysis (bSG)	NA	NA	NA	HR 2 to 6=1.0 (referent), 7=1.4 (1.2–1.6), 8–10=2.2 (1.8–2.8), p<0.001.
Overall survival multivariable analysis (clinical stage)	NA	NA	NA	HR T1c=1.0 (referent), T1ab=1.4 (0.8–2.4), T2a=1.3 (1.1–1.6), T2b=1.3 (1.0–1.6), T2c=1.3 (0.9–1.8), T3=2.3 (1.5–3.3), p-value=0.002.
Overall survival by D'Amico risk classification (low)	NA	NA	NA	HR for EBRT vs. RP: 1.7 (1.3–2.1), p<0.001. HR for BT vs. RP: 1.7 (1.4–2.2), p<0.001.
Overall survival by D'Amico risk classification (intermediate)	NA	NA	NA	HR for EBRT vs. RP: 1.5 (1.2–1.9), p=0.001. HR for BT vs. RP: 1.5 (1.1–2.1), p=0.019.

Table 55. Overall survival (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Overall survival by D'Amico risk classification (high)	NA	NA	NA	HR for EBRT vs. RP: 1.7 (1.3–2.3), p=0.001. HR for BT vs. RP: 3.1 (1.7–5.9), p<0.001.
Albertsen et al. 2007[43] Overall survival (13 years of followup data)	Surgery: 596 patients	Radiation: 642 patients	Observation: 114 patients	Adjusted overall survival curves for the 3 treatment groups. Patients who had surgery were 5 years younger on average and had less comorbidity than patients in the other 2 treatment groups. However, even after adjusting for differences in patient factors and tumor characteristics overall survival in the surgery group was considerable better than for the other 2 groups. Survival differences for the radiation and observation groups were much smaller. The mortality rate ratio was 1.2 (95% CI, 0.9 to 1.5) times higher in the observation versus radiation group.
D'Amico risk group low (overall survival at 13 years followup)	78%	59%	58%	
D'Amico risk group intermediate (overall survival at 13 years followup)	71%	58%	55%	
D'Amico risk group high (overall survival at 13 years followup)	61%	40%	37%	

Table 55. Overall survival (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Abdollah et al. 2011[49]	Radical prostatectomy (RP): 5760 (matched cohort)	Observation: 5,909 patients	NA	Based on the propensity score matched cohort only two estimates were developed: the development cohort (cumulative incidence plots were used) and the external validation cohort (this tested the calibration and discrimination of the multivariate analysis' competing risks nomogram).
Other cause mortality rate at 5 years of followup	7.0% (6.3–7.7)	15.6% (14.6–16.6)	NA	P<0.001
Other cause mortality rate at 10 years of followup	21.5% (20.1–22.9)	37.0% (35.3–38.6)	NA	P<0.001
Other cause mortality multivariate analyses (treatment type)	NA	NA	NA	HR: Observation=1 (reference), RP 0.57 (95% CI, 0.53–0.62), p<0.001
Other cause mortality multivariate analyses (age in years)	NA	NA	NA	HR: 1.10 (95% CI, 1.09–1.11), p<0.001
Other cause mortality multivariate analyses (race Black)	NA	NA	NA	HR: White 1 reference, Black 1.28 (95% CI, 1.12–1.46), p<0.001
Other cause mortality multivariate analyses (race Other)	NA	NA	NA	HR: White 1 reference, Other 0.73 (95% CI, 0.59–0.88), p=0.001
Other cause mortality multivariate analyses (Charlson comorbidity index 1)	NA	NA	NA	HR: 0 reference, 1 1.61 (95% CI, 1.47–1.77), p<0.001
Other cause mortality multivariate analyses (Charlson comorbidity index 2)	NA	NA	NA	HR: 0 reference, 2 1.97 (95% CI, 1.76–2.20), p<0.001
Other cause mortality multivariate analyses (Charlson comorbidity index ≥3)	NA	NA	NA	HR: 0 reference, 3 3.38 (95% CI, 3.03–3.76), p<0.001

Table 55. Overall survival (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Other cause mortality multivariate analyses (clinical stage T2a/b)	NA	NA	NA	HR: T1 reference, T2a/b 1.07 (95% CI, 0.98–1.16), p=0.1
Other cause mortality multivariate analyses (clinical stage T2c)	NA	NA	NA	HR: T1 reference, T2c 1.21 (95% CI, 1.07–1.38), p=0.002
Other cause mortality multivariate analyses (Gleason 6–7)	NA	NA	NA	HR: Gleason score 2–5 reference, Gleason score 6–7 0.84 (95% CI, 0.75–0.94), p=0.002
Other cause mortality multivariate analyses (Gleason 8–10)	NA	NA	NA	HR: Gleason score 2–5 reference, Gleason score 8–10 0.92 (95% CI, 0.80–1.06), p=0.3

Table 56. Prostate cancer–specific mortality (randomized controlled trials)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Wilt et al. 2012[16] Prostate Intervention versus Observation Trial (PIVOT)	Observation: 364 patients	Radical Prostatectomy [RP]: 364 patients	Hazard ratio [HR] (95% confidence interval [CI], p-value for interaction
Overall death from any cause at median followup of 10 years (number of events/total number of patients)	31/367	21/364	0.63 (0.36–1.00)
Age			p=0.63
<65 years	12/131	6/122	0.52 (0.20–1.39)
>65 years	19/236	15/242	0.68 (0.34–3.33)
Race			p=0.76
White	22/220	15/232	0.57 (0.30–1.10)
Black	7/121	5/111	0.80 (0.25–2.54)
Other	2/26	1/21	0.56 (0.05–6.17)
Charlson score			p=0.63
0	19/220	14/224	0.69 (0.34–1.37)
≥1	12/147	7/140	0.54 (0.21–1.38)
Performance score			p=0.57
0	25/310	18/312	0.67 (0.37–1.23)
1–4	6/57	3/52	0.41 (0.10–1.71)
Prostate specific antigen (PSA)			p=0.11
≤10	15/241	14/238	0.92 (0.44–1.91)
>10	16/125	3/52	0.36 (0.15–0.89)
Risk			p=0.11
Low	4/148	6/148	1.48 (0.42–5.24)
Intermediate	13/120	6/129	0.50 (0.21–1.21)
High	14/80	7/77	0.40 (0.16–1.00)
Gleason score			p=0.57
<7	15/261	11/254	0.68 (0.31–1.49)
≥7	15/86	10/98	0.51 (0.23–1.14)

Table 56. Prostate cancer–specific mortality (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Bill-Axelson et al. 2011[25] Same study as Holmberg et al. 2012[54], and Bill-Axelson et al. 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	Watchful waiting: 348 patients	RP: 347 patients	
Total number of deaths due to prostate cancer, cumulative incidence (number (% [95% CI]) at a median followup of 10.8 years (range, 3 weeks–17.2 years)	68 (19.5)	47 (13.5)	
All ages at 8 years followup	9.8 (7.1–13.5)	5.5 (3.5–8.5)	Absolute Reduction Risk (ARR) with RP, % (95% CI): 4.3 (0.4–8.2)
All ages at 12 years followup	17.9 (14.1–22.7)	12.5 (9.2–16.8)	ARR with RP, % (95% CI): 5.4 (-0.2–1.1) Relative Risk (RR) with RP, % (95% CI): 0.65 (0.45–0.94) p=0.03
Age <65 years at 8 years followup	13.3 (9.0–19.6)	5.1 (2.6–10.0)	ARR with RP, % (95% CI): 8.2 (1.9–14.4)
Age <65 years at 12 years followup	23.1 (17.2–30.9)	11.9 (7.5–18.7)	ARR with RP, % (95% CI): 11.2 (2.6–19.8) RR with RP, % (95% CI): 0.5 (0.30–0.84) p=0.014
Age ≥65 years at 8 years followup	6.6 (3.8–11.4)	5.8 (3.3–10.3)	ARR with RP, % (95% CI): 0.8 (-4 .1–5.7)
Age ≥65 years at 12 years followup	13.2 (8.9–19.6)	13.1 (8.8–19.5)	ARR with RP, % (95% CI): 0.1 (-7.3–7.5) RR with RP, % (95% CI): 0.87 (0.51–1.49) p=0.55
Total number of deaths due to prostate cancer, cumulative incidence (number (% [95% CI]) at 15 years followup	81 (23.3)	55 (15.9)	
All at 15 years followup	20.7 (16.7–25.6)	14.6 (11.2–19.10)	ARR with RP, % (95% CI): 6.1 (0.2–12.0) RR with RP, % (95% CI): 0.62 (0.44–0.87) p=0.01

Table 56. Prostate cancer–specific mortality (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Low risk cancer at 15 years followup	11.0 (6.8–17.8)	6.8 (3.5–13.5)	ARR with RP, % (95% CI): 4.2 (-2.9–11.2) RR with RP, % (95% CI): 0.53 (0.24–1.14) p=0.14
Age <65 years at 15 years followup	25.8 (19.7–33.7)	16.4 (11.3–23.8)	ARR with RP, % (95% CI): 9.4 (0.2–18.6) RR with RP, % (95% CI): 0.49 (0.31–0.79) p=0.008
Age <65 years and low risk at 15 years followup	11.6 (6.0–22.4)	7.1 (2.7–18.6)	ARR with RP, % (95% CI): 4.5 (-5.7– 4.8) RR with RP, % (95% CI): 0.41 (0.14–0.17) p=0.14
Age ≥65 years at 15 years followup	16.0 (11.4–22.6)	13.0 (8.9–18.9)	ARR with RP, % (95% CI): 3.0 (-4.3– 0.4) RR with RP, % (95% CI): 0.83 (0.50–0.39) p=0.41
Age ≥65 years and low risk at 15 years followup	10.3 (5.1–21.0)	6.6 (2.5–17.1)	ARR with RP, % (95% CI): 3.8 (-5.9–13.4) RR with RP, % (95% CI): 0.76 (0.25–2.32) p=0.58

Table 56. Prostate cancer–specific mortality (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Jones et al. 2011[26]	External Beam Radiotherapy (EBRT): 992 patients	EBRT plus short-term androgen deprivation therapy (short-term ADT): 987	HR (95% (CI)
Disease-specific mortality at 10 years (% reaching end point)			
All patients	8	4	1.87 (1.27–2.74), p=0.001
Low risk	1	3	0.63 (0.21–1.92)
Intermediate risk	10	3	2.49 (1.50–4.11), p=0.004
High risk	14	12	1.53 (0.72–3.26)
White	8	4	2.33 (1.46–3.72), p<0.001
Black	7	5	1.27 (0.59–2.73)
Age ≤70 years	5	4	1.43 (0.79–2.57)
Age >70 years	10	5	2.19 (1.31–3.64), p=0.004
Widmark et al. 2009[23]	Androgen Deprivation Therapy (ADT): 439 patients	ADT plus EBRT: 436 patients	
Absolute risk reduction in 10 year cumulative incidence of prostate cancer-specific mortally in patients with ONLY T1b–T2	Mean 16.0 (95% CI, 3.7 to 28.2)		
D'Amico et al. 2008[24]	EBRT: 104 patients	EBRT plus Androgen Deprivation Therapy (ADT): 102 patients	
Prostate cancer-specific death in all patients at median followup of 7.6 years (range 0.5–11.0)	14	4	
Prostate cancer-specific death (No or Minimal Comorbidity)	14	3	
Prostate cancer-specific death (Moderate or Severe Comorbidity)	0	1	
	EBRT: 103 patients	EBRT plus ADT: 98 patients	
Prostate cancer-specific death in all patients at median of 4.52 years followup, number of patients	6	0	

Table 57. Prostate cancer–specific mortality (nonrandomized comparative studies)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Abdollah et al. 2012[32]	Radiotherapy: 20,986 patients in propensity score matched cohort	Observation: 20,986 patients in propensity score matched cohort	NA	For patients with low-intermediate risk PC, 10 year Prostate cancer-specific mortality (PCSM) was 3.7% for patients treated with radiotherapy versus 4.1% for patients undergoing observations (p=0.1). For patients with high-risk PC, 10 year PCSM was 8.8% for patients treated with radiotherapy versus 14.4% for patients undergoing observations (p=0.001). In the multivariate analysis, radiotherapy was not an independent predictor of PCSM in patients with low-intermediate risk PC (hazard ratio [HR] 0.91 (0.80 to 1.04), p=0.2). Radiotherapy was an independent risk factor in patients with high-risk PC (HR 0.59 (0.50 to 0.68), p<0.001). Charlson comorbidity index=0: HR 0.81 (0.67–0.98), 0.03 Charlson comorbidity index=1: HR 0.87 (0.75–0.99), p=0.04. Charlson comorbidity index ≥2: HR 0.79 (0.65–0.96), p=0.01. Age 65 to 69 years: HR 0.93 (0.72–1.19) p=0.6 Age 70 to 74 years: HR 0.84 (0.68–1.03) p=0.08 Age 65 to 69 years: HR 0.70 (0.59–0.80) p<0.001
Kibel et al. 2012[31] Adjusted 10-year PCSM	Radical Prostatectomy (RP): 1.8% (95% CI, 1.6–2.1)	External Beam Radiation Therapy (EBRT): 2.9% (95% CI, 2.6–3.3)	Brachytherapy (BT): 2.3% (95% CI, 2.0–2.6)	Kaplan-Meier analysis p-value NR.
Overall PCSM multivariable analysis (treatment group)	1.0 (referent)	1.5 (95% CI, 1.0–2.3)	1.3 (95% CI, 0.7–2.4)	HR p-value: 0.13
Overall PCSM multivariable analysis (patient age)	NA	NA	NA	HR 0.8 (95% CI, 0.5 to 1.3), p=0.065
Overall PCSM multivariable analysis (African-American ethnicity)	NA	NA	NA	HR 0.7 (95% CI, 0.4 to 1.2), p=0.18
Overall PCSM multivariable analysis (comorbidity)	NA	NA	NA	HR none=1.0 (referent); mild 1.2 (0.8–1.7), moderate 1.4 (0.9–2.3), severe 0.7 (0.2–2.9), p=0.4.

Table 57. Prostate cancer–specific mortality (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Overall PCSM multivariable analysis (pretreatment PSA)	NA	NA	NA	HR 1.7 (95% CI, 1.1–2.5), p=0.017.
Overall PCSM multivariable analysis (bSG)	NA	NA	NA	HR 2 to 6=1.0 (referent), 7=2.9 (1.8–4.5), 8 to 10=11.1 (6.5–18.9), p<0.001
Overall PCSM multivariable analysis (clinical stage)	NA	NA	NA	HR T1c=1.0 (referent), T1ab=0.3 (0.1–1.0), T2a=0.4 (0.1–1.5), T2b=0.5 (0.1–1.6), T2c=0.5 (0.1–1.7), T3=0.8 (0.2–2.9), p-value=0.12.
Overall PCSM by D'Amico risk classification (low)	NA	NA	NA	HR for EBRT vs. RP: 1.8 (0.5–6.2), p=0.4. HR for BT vs. RP: 2.3 (0.8–6.9), p=0.14.
Overall PCSM by D'Amico risk classification (intermediate)	NA	NA	NA	HR for EBRT vs. RP: 1.8 (0.8–3.8), p=0.13. HR for BT vs. RP: 0.6 (0.1–2.7), p=0.5.
Overall PCSM by D'Amico risk classification (high)	NA	NA	NA	HR for EBRT vs. RP: 1.3 (0.8–2.1), p=0.2. HR for BT vs. RP: 1.6 (0.4–6.6), p=0.5.
Rosenberg et al. 2012[33] Prostate cancer-specific mortality	BT plus EBRT: 186 patients	BT plus Androgen Deprivation Therapy (ADT): 621 patients	NA	HR Adjusted for age and PC prognostic factors 4.03 (95% CI, 1.17 to 13.89), p=0.027. Estimates of PCSM at 5 years was 3.3% (95% CI, 1.020 to 7.772) in men treated with EBRT and BT compared with 1.1% (95% CI, 0.417 to 2.510) those receiving ADT and brachytherapy.
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for age: 1.086 (95% CI, 0.955–1.235), p=0.21
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for PSA: 8.029 (95% CI, 2.38–28.8), p=0.0014
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for AJCC T category: T1a to c, T2a 1.0 referent, T2b 0.681 (0.092–5.036), p=0.71
Prostate cancer-specific mortality	NA	NA	NA	Multivariate HR adjusted for Gleason score: ≤6=1.0 referent, 3+4: 7.463 (95% CI, 0.816–68.23), p=0.075 4+3: 8.882 (1.095–72.04), p=0.041

Table 57. Prostate cancer–specific mortality (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Shen et al. 2012[42]	BT: 910 patients	BT plus EBRT: 2,466 patients	EBRT: 9,369 patients	A Log rank test was performed for unadjusted comparisons. For multivariate analysis an adjusted HR using the Cox model was created controlling for diagnosis, age, race, urban residence, income, prior malignancy, stage and PSA.
PCSM univariate analysis	NA	NA	NA	Log rank test: PCSM after BT alone or BT plus EBRT was significantly different from EBRT (p<0.001) but there was no difference between BT and BT plus EBRT (p=0.18).
PCSM – multivariate model (year of diagnosis 5 years later)	NA	NA	NA	HR 0.70 (95% CI, 0.63–0.78), p<0.01
PCSM – multivariate model (per year older age)	NA	NA	NA	HR 1.02 (95% CI, 1.01–1.04), p=0.01
PCSM – multivariate model (Asian vs. white)	NA	NA	NA	HR 0.62 (95% CI, 0.49–0.76), p<0.01
PCSM – multivariate model (Black vs. white)	NA	NA	NA	HR 0.93 (95% CI, 0.78–1.10), p=0.38
PCSM – multivariate model (Hispanic)	NA	NA	NA	HR 1.18 (95% CI, 0.95–1.44), p=0.13
PCSM – multivariate model (Urban)	NA	NA	NA	HR 0.99 (95% CI, 0.82–1.20), p=0.93
PCSM – multivariate model (lowest quartile vs. highest quartile income)	NA	NA	NA	HR 1.09 (95% CI, 0.93–1.27), p=0.29
PCSM – multivariate model (low-middle quartile vs. highest quartile income)	NA	NA	NA	HR 0.90 (95% CI, 0.78–1.05), p=0.17
PCSM – multivariate model (low-middle quartile vs. highest quartile income)	NA	NA	NA	HR 0.90 (95% CI, 0.78–1.05), p=0.17
PCSM – multivariate model (high-middle quartile vs. highest quartile income)	NA	NA	NA	HR 1.02 (95% CI, 0.89–1.18), p=0.79
PCSM – multivariate model (prior malignancy vs. prostate only primary)	NA	NA	NA	HR 0.99 (95% CI, 0.82–1.19), p=0.93

Table 57. Prostate cancer–specific mortality (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
PCSM – multivariate model (other malignancy after prostate cancer diagnosis vs. none)	NA	NA	NA	HR 0.73 (95% CI, 0.63–0.86), p<0.01
PCSM – multivariate model (T2 vs. T1)	NA	NA	NA	HR 1.62 (95% CI, 1.39–1.90), p<0.01
PCSM – multivariate model (T3 vs. T1)	NA	NA	NA	HR 2.75 (95% CI, 2.27–3.34), p<0.01
PCSM – multivariate model (PSA elevated)	NA	NA	NA	HR 0.85 (95% CI, 0.63–1.17), p=0.28
PCSM – multivariate model (BT alone vs. EBRT)	NA	NA	NA	HR 0.66 (95% CI, 0.49–0.86), p<0.01
PCSM – multivariate model (BT plus EBRT vs. EBRT)	NA	NA	NA	HR 0.77 (95% CI, 0.66–0.90), p<0.01
Abdollah et al. 2011[49]	Radical Prostatectomy (RP): 5,760 (matched cohort)	Observation: 5,909 patients	NA	Based on the propensity score matched cohort only two estimates were developed: the development cohort (cumulative incidence plots were used) and the external validation cohort (this tested the calibration and discrimination of the multivariate analysis' competing risks nomogram).
PCSM rate at 5 years of followup	0.6% (0.3–0.8)	1.8% (1.4–2.2)	NA	P<0.001
PCSM rate at 10 years of followup	2.8% (2.3–3.4)	5.8% (5.0–6.6)	NA	P<0.001
PCSM multivariate analyses (treatment type)	NA	NA	NA	HR: Observation=1 (reference), RP 0.48 (95% CI, 0.38–0.59), p<0.001
PCSM multivariate analyses (age in years)	NA	NA	NA	HR: 1.04 (95% CI, 1.01–1.07), p=0.006
PCSM multivariate analyses (race Black)	NA	NA	NA	HR: white 1 reference, Black 1.19 (95% CI, 0.84–1.67), p=0.3
PCSM multivariate analyses (race Other)	NA	NA	NA	HR: white 1 reference, Other 0.88 (95% CI, 0.54–1.45), p=0.6
PCSM multivariate analyses (Charlson comorbidity index 1)	NA	NA	NA	HR: 0 reference, 1 1.04 (95% CI, 0.82–1.31), p=0.7
PCSM multivariate analyses (Charlson comorbidity index 2)	NA	NA	NA	HR: 0 reference, 2 0.93 (95% CI, 0.67–1.28), p=0.6
PCSM multivariate analyses (Charlson comorbidity index ≥3)	NA	NA	NA	HR: 0 reference, 3 0.81 (95% CI, 0.57–1.16), p=0.2

Table 57. Prostate cancer–specific mortality (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
PCSM multivariate analyses (clinical stage T2a/b)	NA	NA	NA	HR: T1 reference, T2a/b 1.00 (95% CI, 0.80–1.25), p=0.9
PCSM multivariate analyses (clinical stage T2c)	NA	NA	NA	HR: T1 reference, T2c 1.34 (95% CI, 0.99–1.83), p=0.06
PCSM multivariate analyses (Gleason 6–7)	NA	NA	NA	HR: Gleason score 2 to 5 reference, Gleason score 6–7 2.07 (95% CI, 1.30–3.30), p=0.001
PCSM multivariate analyses (Gleason 8–10)	NA	NA	NA	HR: Gleason score 2–5 reference, Gleason score 8–10 5.89 (95% CI, 3.64–9.54), p<0.001
Hadley et al. 2010[38]	Conservative management : 5,879 patients	Radical Prostatectomy (RP): 11,936 patients	NA	Cox proportional hazards model using three approaches: traditional multivariable survival analysis, propensity score adjustment, and instrumental variable analysis
Multivariable survival analysis	0.036 (0.030–0.041)	0.025 (0.022–0.028	NA	HR 1.59, (1.27–2.00)
Propensity score adjustments (inverse probability of treatment weights [IPTW])	0.035 (0.029–0.040)	0.026 (0.023–0.030)	NA	HR 1.60, (1.40–1.83)
Propensity score adjustments (standardized mortality ratio weights [SMRW])	0.036 (0.030–0.041)	0.030 (0.026–0.033)	NA	HR 1.39 (1.10–1.76)
Instrumental variable approach	0.030 (0.026–0.034)	0.027 (0.023–0.031)	NA	HR 0.73 (0.08–6.73)
Krambeck et al. 2008[28] Death from prostate cancer	Radical Retropubic Prostatectomy (RRP): 0	Robotic-Assisted Radical Prostatectomy (RARP): 0	NA	Median followup time was 1.3 years.
Lu-Yao et al. 2008[36] Prostate specific mortality – all cancer grades combined	Primary androgen deprivation therapy (PADT): 867/32,744 events/person-year, rate per 100=2.6	Conservative management 693/55,424 events/person-year, rate per 100=1.3	NA	Adjusted HR (95% CI,) 1.76 (1.59–1.95) p<0.05

Table 57. Prostate cancer–specific mortality (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
Albertsen et al. 2007[43] Prostate cancer specific survival at 13-years followup	Surgery: 596 patients	Radiation: 642 patients	Observation: 114 patients	Cause specific survival curve for the 3 treatment groups by D'Amico risk category and cause specific survival with standardization via proportional hazards model to average covariate profile in each D'Amico risk group. Competing risk analysis of percent of patients dead of prostate cancer, dead of other causes, and alive in each treatment group 5, 10, and 15 years after diagnosis standardized to age 65 years at diagnosis, average pretreatment comorbidity, Gleason score, PSA and tumor distribution for entire sample.
D'Amico risk category low: Prostate cancer-specific survival at 13-years followup	96%	90%	83%	
D'Amico risk category intermediate: Prostate cancer-specific survival at 13-years followup	92%	80%	89%	
D'Amico risk category high: Prostate cancer–specific survival at 13-years followup	90%	70%	60%	
D'Amico risk category low: Prostate cancer-specific survival at 13-years followup with standardization	96%	90%	83%	
D'Amico risk category intermediate: Prostate cancer-specific survival at 13-years followup with standardization	90%	80%	70%	
D'Amico risk category high: Prostate cancer-specific survival at 13-years followup with standardization	85%	70%	55%	
5-year followup competing risk analysis	Dead of PC: 2% Dead of other causes: 6% Alive: 92%	Dead of PC: 4% Dead of other causes: 5% Alive: 91%	Dead of PC: 6% Dead of other causes: 4% Alive: 90%	

Table 57. Prostate cancer–specific mortality (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Analyses; p-Values
10-year followup competing risk analysis	Dead of PC: 3% Dead of other causes: 14% Alive: 83%	Dead of PC: 9% Dead of other causes: 13% Alive: 78%	Dead of PC: 14% Dead of other causes: 13% Alive: 73%	
15-year followup competing risk analysis	Dead of PC: 8% Dead of other causes: 24% Alive: 68%	Dead of PC: 17% Dead of other causes: 23% Alive: 60%	Dead of PC: 25% Dead of other causes: 20% Alive: 55%	

Table 58. Biochemical failure (randomized controlled trials)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Jones et al. 2011[26]	External Beam Radiotherapy (EBRT): 992 patients	EBRT plus short-term androgen deprivation therapy (short-term ADT): 987 patients	Hazard ratio [HR] (95% confidence interval [CI])
Biochemical failure at 10 years (% reaching end point)	Biochemical failure was defined in the study as an increasing level of prostate specific antigen (PSA)		
All patients	41	26	1.74 (1.48–2.04), p<0.001
Low risk	32	22	1.53 (1.13–2.06), p<0.001
Intermediate risk	45	28	1.79 (1.4–2.21), p<0.001
High risk	53	31	1.98 (1.30–3.03), p=0.002
White	42	29	1.62 (1.35–1.93), p<0.001
Black	40	19	2.27 (1.53–3.38), p<0.001
Age ≤70 years	42	27	1.71 (1.37–2.13), p<0.001
Age >70 years	41	25	1.78 (1.41–2.23), p<0.001
Giberti et al. 2009[21]	Radical retropubic prostatectomy: 100 patients	Brachytherapy: 100 patients	
5-year biochemical disease-free survival rate (%)	Biochemical failure was defined as two consecutive PSA values ≥0.2 ng/mL. 91%	Biochemical failure was defined as a PSA increase ≥2 ng/mL higher than the PSA nadir value independent of the serum concentration of the nadir. 91.7%	
D'Amico et al. 2008[24]	EBRT: 103 patients	EBRT plus Androgen Deprivation Test (ADT): 98 patients	HR (95% CI)
PSA failure at median of 4.52 years followup, number of patients	43	21	2.86 (1.69–4.86), p<0.001

Table 59. Biochemical failure (nonrandomized comparative studies)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Krambeck et al. 2008[28] PSA progression	Radical retropubic prostatectomy (RRP): 32 patients	Robotic-assisted radical prostatectomy (RARP): 14 patients	Median followup time was 1.3 years.
Clinical local recurrence	RRP: 5	RARP: 3	Median followup time was 1.3 years. Groups were similar on margin positivity.

Table 60. Biochemical progression–free survival (randomized controlled trials)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Martis et al. 2007[65]	Radical Perineal Prostatectomy: 100 patients	Radical Retropubic Prostatectomy: 100 patients	
Percentage of patients with negative 1-hour pad-test at 6 months followup	74	75	
Percentage of patients with negative 1-hour pad-test at 24 months followup	96	95	

Table 61. Biochemical progression–free survival (nonrandomized comparative studies)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Krambeck et al. 2008[28] PFS (% free of PSA progression)	Radical Retropubic Prostatectomy (RRP): Mean (SEM) 92.2% (1.8%)	Robotic-Assisted Radical Prostatectomy (RARP): Mean 92.4 % (2.3%)	3 year Kaplan Meier PFS. PFS was similar between groups.
Barocas et al. 2010[27]	RRP: 83,5 (78.3 to 87.5)	RALP: 84.0 (79.4–87.7)	3 year recurrence free survival (95% CI) log rank p value=0.19 showing no between group difference.
Schroeck et al. 2008[29] Cox model adjusted for clinical variables (PSA, clinical stage, biopsy, Gleason score, age, race, BMI, and year of surgery). Mean followup was 1.37 years for RRP and 1.09 years for RALP.	RRP: 435 patients	RALP: 362 patients	HR and (95% CI) for PSA recurrence free survival Cox regression models. HR 0.82 (0.48 to 1.38), p=0.448 There was no between group difference in PSA recurrence free survival.
Cox model adjusted for risk category. Mean followup was 1.37 years for RRP and 1.09 years for RALP.	RRP: 435 patients	RALP: 362 patients	HR and (95% CI) for PSA recurrence free survival Cox regression models. HR 0.87 (0.52–1.47), p=0.610
Cox model adjusted for clinical and pathological variables (PSA, clinical stage, biopsy Gleason score, age, race, BMI, year of surgery, prostate weight, pathological stage, and pathological Gleason score). Mean followup was 1.37 years for RRP and 1.09 years for RALP.	RRP: 435 patients	RALP: 362 patients	HR and (95% CI) for PSA recurrence free survival Cox regression models. HR 0.94 (0.55–1.61), p=0.824

Table 62. Progression to metastasis (randomized controlled trials)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Wilt et al. 2012[16] Prostate Intervention versus Observation Trial (PIVOT)	Radical prostatectomy (RP): 364 patients	Observation: 367 patients	
Number of men with bone metastases (%) at median followup 10 years	17 (4.7)	39 (10.0)	Hazard ratio [HR], 0.40; 95% confidence interval [CI], 0.22–0.70; p<0.002.
Bill-Axelson et al. 2011[25] Same study as Holmberg et al. 2012[54], and Bill-Axelson et al. 2008[46] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	Watchful waiting: 348 patients	RP: 347 patients	
Total number of distant metastases, cumulative incidence (number (%, [95% CI at a followup of 12 years	96 (27.6)	67 (19.3)	
All ages at 8 years followup	18.7 (15–23.3)	11.5 (8.6–15.4)	Absolute risk reduction (ARR), 95% CI: 7.2 (1.8–12.5)
All ages at 12 years followup	26 (21.6–31.2)	19.3 (15.3–24.2)	ARR: 6.7 (0.2–13.2) Relative risk (RR): 0.65 (0.47–0.88) p=0.006
Age <65 years at 8 years followup	22.9 (17.3–30.3)	10.8 (6.9–17)	ARR: 12.1 (4.0–20.1)
Age <65 years at 12 years followup	30.3 (23.8–38.5)	20.7 (15–28.6)	ARR: 9.6 (-0.3–19.5) RR: 0.52 (0.34–0.81) p=0.006
Age ≥65 years at 8 years followup	14.8 (10.5–21)	12.1 (8.2–17.8)	ARR: 2.7 (-4.2–9.7)
Age ≥65 years at 12 years followup	22 (16.5–29.3)	17.9 (13–24.6)	ARR: 4.1 (16.5–29.3) RR: 0.80 (0.51–1.27) p=0.28
Total number of distant metastases (number (%, [95% CI]) at 15 years followup	123 (35.3)	81 (23.3)	
All at 15 years followup	33.4 (28.6–39.0)	21.7 (17.6–26.7)	ARR: 11.7 (4.8–18.6) RR: 0.59 (0.45–0.79) p<0.001
Low risk cancer at 15 years followup	21.4 (15.4–29.6)	9.9 (5.8 - 17.1)	ARR: 11.4 (2.6–20.2) RR: 0.43 (0.23–0.79) p=0.008

Table 62 Progression to metastasis (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Age <65 years at 15 years followup	39.8 (32.6–48.5)	21.5 (15.9–29.2)	ARR: 18.3 (8.0–28.5) RR: 0.47 (0.32–0.70) p=0.001
Age <65 years and low risk cancer at 15 years followup	20.6 (12.8–33.0)	9.5 (4.4–20.4)	ARR: 11.1 (-1.0–23.2) RR: 0.41 (0.18–0.95) p=0.06
Age ≥65 years at 15 years followup	27.5 (21.5–35.1)	22.1 (16.6–29.4)	ARR: 5.4 (-3.9–14.6) RR: 0.77 (0.51–1.15) p=0.14
Age ≥65 years and low risk cancer at 15 years followup	21.8 (13.9–34.3)	10.5 (4.8–23.0)	ARR: 11.3 (-1.6–24.1) RR: 0.46 (0.19–1.11) p=0.06
Jones et al. 2011[26]	External Beam Radiation Therapy (EBRT): 992 patients	EBRT plus Androgen Deprivation Therapy (ADT): 987 patients	Hazard Ratio [HR] (95% [CI])
Distant metastases at 10 years (% reaching end point)			
All patients	8	6	1.45 (1.03–2.06), p=0.04

Table 63. Progression to metastasis (nonrandomized comparative studies)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-values
Krambeck et al. 2008[28] Systemic progression	Radical Retropubic Prostatectomy (RRP): 0	Robotic-Assisted Radical Prostatectomy (RARP): 1	Median followup time was 1.3 years.

Table 64. Quality of life (randomized controlled trials)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Johansson et al. 2011[47] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	Watchful waiting [WW] n/total number of patients who provided information for each question	Radical Prostatectomy [RP] n/total number of patients who provided information for each question	Age-adjusted relative risk, RP vs. WW (95% confidence interval [CI]
Anxiety (moderate or high) at median followup of 12.2 years (range 7–17)	69/161 (43%)	77/178 (43%), mean 2.74	0.97 (0.76–1.24)
Depressed mood (moderate or high) at median followup of 12.2 years (range 7–17)	82/159 (52%)	85/180 (47%), mean 2.89	0.92 (0.74–1.14)
Wellbeing (high) at median followup of 12.2 years (range 7–17)	71/161 (44%), mean 5.04	73 /179 (41%), mean 5.11	0.89 (0.70–1.13)
Quality of life (high) at median followup of 12.2 years (range 7–17)	55/160 (34%), mean 5.00	62/179 (35%), mean 4.96	0.98 (0.73–1.31)
Sense of meaningfulness (moderate or high) at median followup of 12.2 years (range 7–17)	79/160 (49%), mean 5.33	83/179 (46%), mean 5.32	0.92 (0.74–1.15)
Jones et al. 2011[26]	External Beam Radiotherapy (EBRT): 274 patients (number/total number (%)	EBRT plus short-term androgen deprivation therapy (short-term ADT): 284 patients (number/total number (%)	
Effect of short-term ADT on erectile function, according to responses on the Sexual Adjustment Questionnaire at 1 year [number (%)]			
Always or almost always	85 (31)	59 (21)	p=0.004
Sometimes	62 (23)	66 (23)	p=0.95
Almost never or never	69 (25)	94 (33)	p=0.054
Did not try	55 (20)	58 (20)	p=1.00
Not applicable or not answered	4 (1)	13 (5)	p=0.04

Table 64. Quality of life (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Giberti et al. 2009[21]	Radical Retropubic Prostatectomy: 100 patients	Brachytherapy: 100 patients	
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)-C30 at 5-year followup			
Physical function	90	94	p-value not specified
Role function	90	94	p-value not specified
Emotional function	84	82	p-value not specified
Cognitive function	90	88	p-value not specified
Social function	89	94	p-value not specified
Global health/Quality of life (QOL)	78	82	p-value not specified
Fatigue	18	18	p-value not specified
Nausea/vomiting	1	1	p-value not specified
Pain	9	8	p-value not specified
Dyspnea	8	11	p-value not specified
Insomnia	22	20	p-value not specified
Appetite loss	3	4	p-value not specified
Constipation	3	0	p-value not specified
Diarrhea	5	6	p-value not specified
Financial problem	3	2	p-value not specified
International Prostate Symptom Score (IPSS) at 5-year followup	4.7	5.1	p-value not specified
EORTC-QLQ-PR25 urinary symptoms	10	17	p-value not specified
Bowel symptoms	2	5	p-value not specified
Treatment-related symptoms	8	8	p-value not specified
Sexual function	7	8	p-value not specified
Sexual activity	8	8	p-value not specified
International Index of Erectile Function (IIEF) at 5-year followup	22.0	21.2	p-value not specified

Table 64. Quality of life (randomized controlled trials) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Analyses; p-Values
Martis et al. 2007[22]	Radical Perineal Prostatectomy: 100 patients	Radical Retropubic Prostatectomy: 100 patients	
IIEF score at 6 months followup	30% of the patients had an average score of 18.5±0.5	45% of the patients had an average score of 21.7±1.9	
IIEF score at 24 months followup	42% had a an average score of 19.7±1.1	60% had a an average score of 23.1±2.5	

Table 65. Quality of life (nonrandomized comparative studies)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Ferrer et al. 2007[30]	Radical prostatectomy (RP): 134 patients	3D conformal radiotherapy (3D-CRT): 205 patients	Brachytherapy: 275 patients	NA	One-way analysis of variance of Heath related Quality of Life (HRQL) scores (mean and SE) by treatment and risk group at the 2 year followup
SF-36 physical component summary	50.6 (0.8)	49.2 (0.6)	50.9 (0.5)	NA	p>0.05 at the 24 month followup for all dimensions forming the physical component. P=0.094 for component summary.
SF-36 mental component summary	54.9 (0.8)	56.3 (0.5)	56.3 (0.4)	NA	p>0.05 at the 24 month followup for all dimensions forming the mental component. P=0.373 for component summary.
Functional Assessment of Cancer Therapy General (FACT-G)	76.6 (1.1)	77.5 (0.9)	79.8 (0.6)	NA	One dimension of the FACT-G (physical well-being) showed significant between group differences for RP vs. brachytherapy and brachytherapy vs. 3D-CRT (p<0.05) at the 24 month followup. For entire scale, p=0.008 for RP vs. brachytherapy.
Functional Assessment of Cancer Therapy Prostate Specific (FACT-P)	37.2 (0.5)	37.5 (0.4)	38.9 (0.3)	NA	For the entire scale, p=0.001 for RP vs. brachytherapy and for brachytherapy vs. 3D CRT.
American Urologic Association Symptom Index (AUA-7)	4.9 (0.6)	6.4 (0.5)	5.7 (0.4)	NA	P=0.405

Table 65. Quality of life (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Expanded Prostate Cancer Index Composite (EPIC urinary)	88.2 (1.3)	94.2 (0.8)	92.4 (0.8)	NA	For the following subscale scores there was a significant (p<0.05) between group difference at the 24 month follow up for RP vs. brachytherapy: irritative obstructive, urinary function, sexual function, incontinence, and sexual bother. For the following subscale scores there was a significant (p<0.05) between group difference at the 24 month follow up for brachytherapy vs. 3D conformal radiotherapy: bowel function, sexual function, and bowel bother. Overall p values for EPIC urinary (p<0.001 RP vs. both other treatments), urinary irritative (p=0.005 for RP vs. brachytherapy), urinary incontinence (p<0.001 for RP vs. both other treatments), EPIC bowel (p<0.001 3D conformal radiotherapy vs. both other treatments), EPIC sexual (p<0.001 for all comparisons), EPIC hormonal (p=0.74).
Urinary irritative	NR	NR	NR	NA	
Urinary incontinence	NR	NR	NR	NA	
EPIC bowel	97.9 (0.7)	94.5 (0.9)	97.9 (0.3)	NA	
EPIC sexual	33.1 (2.1)	43.5 (1.9)	49.8 (1.6)	NA	
EPIC hormonal	93.7 (1.0)	93.7 (0.9)	95.5 (0.5)	NA	

Table 65. Quality of life (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Resnick et al. 2013[44]	Prostatectomy	Radiotherapy	NA	NA	Odds Ratio (95% CI) for prostatectomy versus radiotherapy, adjusted for registry, baseline function, race or ethnicity, tumor grade, number of coexisting illnesses, education, and propensity score.
No control or frequent urinary leakage at the 2-year followup	9.6%	3.2%	NA	NA	6.22 (1.92-20.29)
No control or frequent urinary leakage at the 5-year followup	13.4%	4.4%	NA	NA	5.10 (2.29-11.36)
No control or frequent urinary leakage at the 15-year followup	18.3%	9.4%	NA	NA	2.34 (0.88-6.23)
Bothered by dripping or leaking urine at the 2-year followup	10.6%	2.4%	NA	NA	5.86 (1.93-17.64)
Bothered by dripping or leaking urine at the 5-year followup	12.9%	2.9%	NA	NA	7.66 (2.97-19.89)
Bothered by dripping or leaking urine at the 15-year followup	17.1%	18.4%	NA	NA	0.87 (0.41-1.80)
Erection insufficient for intercourse at the 2-year followup	78.8%	60.8%	NA	NA	3.46 (1.93-6.17)
Erection insufficient for intercourse at the 5-year followup	75.7%	71.9%	NA	NA	1.96 (1.05-3.63)
Erection insufficient for intercourse at the 15-year followup	87.0%	93.9%	NA	NA	0.38 (0.12-1.22)
Bothered by sexual dysfunction at the 2-year followup	55.5%	48.2%	NA	NA	1.19 (0.77-1.86)

Table 65. Quality of life (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Bothered by sexual dysfunction at the 5-year followup	46.7%	39.7%	NA	NA	1.48 (0.92-2.39)
Bothered by sexual dysfunction at the 15-year followup	43.5%	35.8%	NA	NA	1.33 (0.58-3.03)
Bowel urgency at the 2-year followup	13.6%	34.0%	NA	NA	0.39 (0.22-0.68)
Bowel urgency at the 5-year followup	16.3%	31.3%	NA	NA	0.47 (0.26-0.84)
Bowel urgency at the 15-year followup	21.9%	35.8%	NA	NA	0.98 (0.45-2.14)
Bothered by frequent bowel movements, pain, or urgency at the 2-year followup	2.9%	7.9%	NA	NA	0.37 (0.14-0.96)
Bothered by frequent bowel movements, pain, or urgency at the 5-year followup	4.4%	5.8%	NA	NA	0.93 (0.27-3.22)
Bothered by frequent bowel movements, pain, or urgency at the 15-year followup	5.2%	16.0%	NA	NA	0.29 (0.11-0.78)

Table 65. Quality of life (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Malcolm et al. 2010[34]	Open radical prostatectomy (ORP)	Robotic-assisted prostatectomy (RAP)	Brachytherapy (BT)	Cryotherapy	Cox proportional hazards ratio adjusted for age, race, Gleason score and baseline functioning on this outcome. Results are presented as hazard ratio (95% CI) for returning to 90% of the baseline score. Scores are presented as average percent baseline scores (PBS)
Urinary function	PBS at 1 year followup: 79 PBS at 2 year followup: 84 PBS at 3 year followup: 83	PBS at 1 year followup: 74 PBS at 2 year followup: 76 PBS at 3 year followup: 78	PBS at 1 year followup: 94 PBS at 2 year followup: 90 PBS at 3 year followup: 88	PBS at 1 year followup: 106 PBS at 2 year followup: 102 PBS at 3 year followup: 113	ORP plus RAP 1.0, BT plus Cryotherapy 2.98 (2.33-3.82)
Urinary bother	PBS at 1 year followup: 84 PBS at 2 year followup: 87 PBS at 3 year followup: 88	PBS at 1 year followup: 81 PBS at 2 year followup: 83 PBS at 3 year followup: 86	PBS at 1 year followup: 88 PBS at 2 year followup: 94 PBS at 3 year followup: 90	PBS at 1 year followup: 97 PBS at 2 year followup: 98 PBS at 3 year followup: 103	ORP plus RAP 1.0, BT plus Cryotherapy 1.48 (1.17-1.88)
Sexual function	PBS at 1 year followup: 43 PBS at 2 year followup: 46 PBS at 3 year followup: 48	PBS at 1 year followup: 40 PBS at 2 year followup: 45 PBS at 3 year followup: 46	PBS at 1 year followup: 71 PBS at 2 year followup: 74 PBS at 3 year followup: 73	PBS at 1 year followup: 30 PBS at 2 year followup: 36 PBS at 3 year followup: 27	ORP, RAP, plus cryotherapy 1, BT 5.71 (3.71-8.77)
Sexual bother	PBS at 1 year followup: 40 PBS at 2 year followup: 52 PBS at 3 year followup: 58	PBS at 1 year followup: 47 PBS at 2 year followup: 48 PBS at 3 year followup: 45	PBS at 1 year followup: 63 PBS at 2 year followup: 78 PBS at 3 year followup: 85	PBS at 1 year followup: 59 PBS at 2 year followup: 61 PBS at 3 year followup: 50	ORP plus RAP 1, BT plus cryotherapy 1.99 (1.49-2.67)

Table 65. Quality of life (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Bowel function	PBS at 1 year followup: 102 PBS at 2 year followup: 104 PBS at 3 year followup: 101	PBS at 1 year followup: 103 PBS at 2 year followup: 101 PBS at 3 year followup: 102	PBS at 1 year followup: 103 PBS at 2 year followup: 110 PBS at 3 year followup: 107	PBS at 1 year followup: 110 PBS at 2 year followup: 108 PBS at 3 year followup: 108	BT 1, ORP, RAP, plus cryotherapy 1.24 (0.99 to 1.55)
Bowel bother	PBS at 1 year followup: 99 PBS at 2 year followup: 102 PBS at 3 year followup: 99	PBS at 1 year followup: 100 PBS at 2 year followup: 97 PBS at 3 year followup: 94	PBS at 1 year followup: 99 PBS at 2 year followup: 101 PBS at 3 year followup: 99	PBS at 1 year followup: 106 PBS at 2 year followup: 107 PBS at 3 year followup: 92	ORP, BT plus cryotherapy 1, RAP 1.28 (1.08 to 1.51)

Table 65. Quality of life (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Krambeck et al. 2008[28]	Radical retropubic prostatectomy (RRP): 564 patients	Robotic assisted radical prostatectomy (RARP): 286 patients	NA	NA	N (%) with early (1 month) and late (>1 month) post-surgical complications based on patients treated in the matched comparison study.
Any early complication	27 (4.8%)	23 (8.0%)	NA	NA	P=0.064
Bladder neck contracture	1 (0.2%)	0 (0%)	NA	NA	P=0.476
Hemorrhage/hematoma	10 (1.8%)	10 (3.5%)	NA	NA	P=0.150
Hernia	0 (0%)	3 (1%)	NA	NA	P=0.038
Renal failure	1 (0.2%)	0 (0%)	NA	NA	P=0.476
Sepsis	1 (0.2%)	0 (0%)	NA	NA	P=0.476
Stricture	3 (0.5%)	2 (0.7%)	NA	NA	P=0.763
Ureteric obstruction	1 (0.2%)	0 (0%)	NA	NA	P=0.476
Urinary retention	7 (1.2%)	8 (2.8%)	NA	NA	P=0.104
UTI	6 (1.1%)	3 (1%)	NA	NA	P=0.984
Deep vein thrombosis	7 (1.2%)	1 (0.3%)	NA	NA	P=0.203
Drug reaction	7 (1.2%)	2 (0.7%)	NA	NA	P=0.466
Ileus	10 (1.8%)	5 (1.7%)	NA	NA	P=0.982
Lymphocele	4 (0.7%)	2 (0.7%)	NA	NA	P=0.987
Lymphedema	1 (0.2%)	0 (0%)	NA	NA	P=0.476
Myocardial infarction	0 (0%)	0 (0%)	NA	NA	NA
Pulmonary embolism	4 (0.7%)	1 (0.3%)	NA	NA	P=0.517
Respiratory failure	3 (0.5%)	2 (0.7%)	NA	NA	P=0.763
Requiring transfusion	77 (13.1%)	15 (5.1%)	NA	NA	P<0.001
Stroke	3 (0.5%)	3 (1%)	NA	NA	P=0.395
	RRP: 492 patients with one year followup	RARP: 248 patients with one year followup			
Abdominal abscess	2 (0.4%)	0 (0%)	NA	NA	P=0.554
Bladder neck contracture	23 (4.6%)	3 (1.2%)	NA	NA	P=0.018
Deep vein thrombosis	6 (1.2%)	1 (0.4%)	NA	NA	P=0.434
Hernia	14 (2.8%)	10 (4.0%)	NA	NA	P=0.387
Lymphocele	5 (1.0%)	1 (0.4%)	NA	NA	P=0.670

Table 65. Quality of life (nonrandomized comparative studies) (continued)

Study Outcomes	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4	Analyses; p-Values
Lymphedema	0 (0%)	0 (0%)	NA	NA	NA
Pulmonary embolism	5 (1.0%)	0 (0%)	NA	NA	P=0.175
Urethral stricture	6 (1.2%)	8 (3.2%)	NA	NA	P=0.083
	RRP: 496 patients with one year data for continence and potency	RARP: 252 patients with one year data for continence and potency	NA	NA	P=0.344
With continence	446 (93.7%)	224 (91.8%)	NA	NA	NA
Continence=No pads	419 (88.0%)	199 (81.6%)	NA	NA	NA
Continence=security pad only	27 (5.7%)	25 (10.3%)	NA	NA	NA
Without continence	30 (6.3%)	20 (8.2%)	NA	NA	NA
Continence=1 to 2 pads per day	23 (4.8%)	17 (7.0%)	NA	NA	NA
Continence=3 pads per day	7 (1.5%)	3 (1.2%)	NA	NA	NA
Previous incontinence	6	1	NA	NA	NA
Continence=unknown	14	7	NA	NA	NA
	RRP: 496 patients with potency data at one year followup	RARP: 252 patients with potency data at the one year followup	NA	NA	P=0.081
Impotent	155 (37.2)	61 (30%)	NA	NA	NA
Potent	262 (62.8%)	142 (70%)	NA	NA	NA
Previously impotent	49	32	NA	NA	NA
Potency=unknown	31	17	NA	NA	NA

Table 66. Reported adverse events (randomized controlled trials)

Study	Adverse Events/Harms Reported		Risk Ratio or Relative Risk (95% Confidence Interval)
Wilt et al. 2012[16] Prostate Intervention versus Observation Trial (PIVOT)	Adverse events occurring within 30 days after surgery	Patients (N=280) N (%)	
	Any	60 (21.4)	
	Pneumonia	2 (0.7)	
	Wound infection	12 (4.3)	
	Urinary tract infection	7 (2.5)	
	Sepsis	3 (1.1)	
	Deep vein thrombosis	2 (0.7)	
	Stroke	1 (0.4)	
	Pulmonary embolism	2 (0.7)	
	Myocardial infarction	3 (1.1)	
	Renal failure or dialysis	1 (0.4)	
	Bowel injury requiring surgical repair	3 (1.1)	
	Additional surgical repair	7 (2.5)	
	Bleeding requiring transfusion	6 (2.1)	
	Urinary catheter present >30 days after surgery	6 (2.1)	
	Death	1 (0.4)	
	Other	28 (10.0)	
	Patient-Reported Urinary, Erectile, and Bowel Dysfunction at 2 Years (number of events/total number of patients) Urinary Incontinence: Radical Prostatectomy (RP): 49/287 (17.1%) Observation 18/284 (6.3%) P<0.001 Erectile dysfunction: RP: 231/285 (81.1%) Observation: 124/281 (44.1%) P<0.001 Bowel dysfunction: RP: 35/286 (12.2%) Observation: 32/282 (11.3) P=0.74		

Table 66. Reported adverse events (randomized controlled trials) (continued)

Study	Adverse Events/Harms Reported		Risk Ratio or Relative Risk (95% Confidence Interval)
Bill-Axelson et al. 2011[25] Scandinavian Prostate Cancer Group-4 (SPCG-4) Trial	Nonfatal Surgical Complications within 1 year after Surgery among Men in the RP (N=289) Group		
	Complication	*Number of Events*	*1-Year Cumulative Incidence (95% confidence interval [CI]*
	Urinary leakage	93	32.2 (27.2–38.1)
	Urinary obstruction	6	2.1 (0.9–4.6)
	Impotence	168	58.1 (52.7–64.1)
	Pulmonary embolism	4	1.4 (0.5–3.7)
	Deep vein thrombosis	3	1.0 (0.3–3.2)
	Myocardial infarction	0	Not applicable
	Endpoint in the trial analyzed according to intention to treat		
	Endpoint	Result by intention to treat	Median followup
	Prevalence of erectile dysfunction	Watchful Waiting [WW]: 45% RP: 49% Relative Risk (RR) 95% confidence interval [CI] for RP vs. WW: 2.3 (1.6–3.2)	4 years
	Prevalence of urinary leakage	WW: 21% RP: 49% RR for RP vs. WW: 2.3 (1.6–3.2)	4 years

Table 66. Reported adverse events (randomized controlled trials) (continued)

Study	Adverse Events/Harms Reported		Risk Ratio or Relative Risk (95% Confidence Interval)
Giberti et al. 2009[21]	Radical retropubic prostatectomy: 100 patients	Brachytherapy: 100 patients	
Urinary incontinence	18.4% (severe in 5.4% and mild in 13.0%) at 6-month-followup	Not reported	
Anastomotic urethral stricture	6.5% at 6-month-followup	Not reported	
Irritative urinary symptoms	5.0% at 6-month-followup	80% at 6-month followup 20% at 1-year followup	
Erectile function	Significant worsening of the QLQ-PR25 and IIEF was reported by both groups at 6-month-followup		
Erectile function and urinary disorders at 5-year followup.	There was no differences in erectile function and urinary disorders at the 5-year followup period in both study groups.		
Jones et al. 2011[26]	External Beam Radiotherapy (EBRT): 992 patients	EBRT plus Androgen Deprivation Therapy (ADT): 987	
Incidence of grade 3 or higher acute and late gastrointestinal toxic effects up to 90 days after the start of EBRT	3%	1%	
Acute grade 3 of higher genitourinary toxic effects up to 90 days after the start of EBRT	2%	2%	
Deaths	Colonic obstruction: 2 patients	Colorectal bleeding: 1 patient	

Table 66. Reported adverse events (randomized controlled trials) (continued)

Study	Adverse Events/Harms Reported		Risk Ratio or Relative Risk (95% Confidence Interval)
D'Amico et al. 2008[24]	EBRT: 103 patients at median followup of 4.52 years	EBRT plus Androgen Suppression Therapy (ADT): 98 patients at median followup of 4.52 years	
	Urinary incontinence (complete)	Grade 1: 3	Grade 1: 2
		Grade 2: 1	Grade 2: 1
		Grade 3: 1	Grade 3: 1
		Grade 4: 0	Grade 4: 0
	Urinary incontinence (stress)	Grade 1: 20	Grade 1: 22
		Grade 2: 7	Grade 2: 6
		Grade 3: 0	Grade 3: 0
		Grade 4: 0	Grade 4: 0
	Hematuria	Grade 1: 6	Grade 1: 7
		Grade 2: 5	Grade 2: 6
		Grade 3: 3	Grade 3: 3
		Grade 4: 0	Grade 4: 0
	Diarrhea	Grade 1: 19	Grade 1: 18
		Grade 2: 8	Grade 2: 9
		Grade 3: 3	Grade 3: 1
		Grade 4: 0	Grade 4: 0
	Rectal bleeding	Grade 1: 34	Grade 1: 26
		Grade 2: 18	Grade 2: 16
		Grade 3: 2	Grade 3: 3
		Grade 4: 0	Grade 4: 0
	Anal fibrosis	Grade 1: 1	Grade 1: 1
		Grade 2: 0	Grade 2: 0
		Grade 3: 0	Grade 3: 0
		Grade 4: 0	Grade 4: 0
	Impotence	Grade 1: 4	Grade 1: 1
		Grade 2: 7	Grade 2: 6
		Grade 3: 21	Grade 3: 26
		Grade 4: 0	Grade 4: 0
	Gynecomastia	Grade 1: 1	Grade 1: 14
		Grade 2: 2	Grade 2: 4
		Grade 3: 0	Grade 3: 0
		Grade 4: 0	Grade 4: 0
	Liver dysfunction	Grade 1: 0	Grade 1: 0
		Grade 2: 0	Grade 2: 0
		Grade 3: 1	Grade 3: 0
		Grade 4: 1	Grade 4: 0

Table 66. Reported adverse events (randomized controlled trials) (continued)

Study	Adverse Events/Harms Reported			Risk Ratio or Relative Risk (95% Confidence Interval)
Martis et al. 2007[22]		Radical Perineal Prostatectomy: 100 patients	Radical Retropubic Prostatectomy: 100 patients	p-Value
	Urinary continence at 6 months (number, %)	74 (74)	76 (76)	p=0.85
	Urinary continence at 24 months (number, %)	96 (96)	95 (95)	p=1
	Erectile function at 6 months (number, %)	30 (30)	45 (45)	p=0.07
	Erectile function at 2 4 months (number, %)	42 (42)	60 (60)	p=0.03

Table 67. Reported adverse events (nonrandomized comparative studies)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Barry et al. 2012[35]	Incontinence (moderate or big problem)	Robotic-assisted laparoscopic radical prostatectomy (RALRP) patients (131/393) Open retropubic radical prostatectomy (ORRP) patients (58/214)	Pearson chi-square p-value=0.113 for the between group difference in incontinence. A logistic regression model controlling for age and education was performed comparing RALRP to ORRP, producing an OR 1.41 (95% CI, 0.97–2.05). A second logistic regression model with mental and overall health factored in in addition to age and education produced an OR of 1.46 (95% CI, 1.00–2.12, p=0.049). Confirmatory ordinal regression models found RALRP to be significantly associated with greater degrees of problems with continence in both the age, education adjusted model (p=0.020) and the four control variable model (p=0.007).
	Sexual dysfunction (moderate or big problem)	RALRP patients (335/383) ORRP patients (187/210)	Pearson chi-square p-value=0.57 for the between group difference in incontinence. A logistic regression model controlling for age and education was performed comparing RALRP to ORRP, producing an OR 0.87 (95% CI, 0.51–1.49). A second logistic regression model with mental and overall health factored in in addition to age and education produced an OR of 0.93 (95% CI, 0.54–1.61). Confirmatory ordinal regression models found RALRP not to be significantly associated with greater degrees of sexual dysfunction in both the age and education adjusted model (p=0.605) and the four control variable model (p=0.761).
Mohammed et al. 2012[39]	Acute dysuria ≥Grade 2	Brachytherapy (BT): 9%	p-value of difference: <0.001
		Image-guided radiation therapy (EB-IGRT): 8%	
		EBRT plus high-dose rate (HDR): 25%	
	Acute Frequency ≥Grade 2	BT: 27%	p-value of difference:< 0.001
		EB-IGRT: 39%	
		EBRT plus HDR: 38%	
	Acute retention ≥Grade 2	BT: 13%	p-value of difference: <0.001
		EB-IGRT: 6%	
		EBRT plus HDR: 6%	
	Acute Hematuria ≥Grade 2	BT: 0%	p-value of the difference: =0.04
		EB-IGRT: 3%	
		EBRT plus HDR: 0.6%	

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Mohammed et al. 2012[39] (continued)	Acute Incontinence ≥Grade 2	BT: 2%	p-value of the difference: =0.65
		EB-IGRT: 2%	
		EBRT plus HDR: 1%	
	Any acute genitourinary toxicity ≥Grade 2	BT: 35%	p-value of difference: <0.001
		EB-IGRT: 43%	
		EBRT plus HDR: 50%	
	Late dysuria ≥Grade 2	BT: 4%	p-value of difference: <0.001
		EB-IGRT: 0.5%	
		EBRT plus HDR: 3%	
	Late Frequency/urgency ≥Grade 2	BT: 18%	p-value of difference: 0.26
		EB-IGRT: 14%	
		EBRT plus HDR: 17%	
	Late retention Grade 2	BT: 9%	p-value of difference: <0.001
		EB-IGRT: 3%	
		EBRT plus HDR: 12%	
	Late Hematuria ≥Grade 2	BT: 5%	p-value of difference: 0.12
		EB-IGRT: 7%	
		EBRT plus HDR: 4%	
	Late Incontinence ≥Grade 2	BT: 2%	p-value of difference: 0.17
		EB-IGRT: 3%	
		EBRT plus HDR: 5%	
	Late urethral stricture	BT: 4%	p-value of difference: <0.001
		EB-IGRT: 2%	
		EBRT plus HDR: 11%	
	Any late genitourinary toxicity ≥Grade 2	BT: 22%	p-value of difference: 0.01
		EB-IGRT: 21%	
		EBRT plus HDR: 28%	
	Acute dysuria ≥Grade 3	BT: 1%	p-value of difference: <0.001
		EB-IGRT: 0%	
		EBRT plus HDR: 2%	

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Mohammed et al. 2012[39] (continued)	Acute frequency ≥Grade 3	BT: 7%	p-value of difference: 0.002
		EB-IGRT: 3%	
		EBRT plus HDR: 5%	
	Acute retention ≥Grade 3	BT: 2%	p-value of difference: 0.11
		EB-IGRT: 0.6%	
		EBRT plus HDR: 1%	
	Acute hematuria ≥Grade 3	BT: 0%	p-value of difference: 0.62
		EB-IGRT: 0.3%	
		EBRT plus HDR: 0%	
	Acute incontinence ≥Grade 3	BT: 0.3%	p-value of difference: 0.62
		EB-IGRT: 0.2%	
		EBRT plus HDR: 0%	
	Acute any acute genitourinary ≥Grade 3	BT: 8%	p-value of difference: 0.001
		EB-IGRT: 4%	
		EBRT plus HDR: 7%	
	Acute diarrhea ≥Grade 3	BT: 0.3%	p-value of difference: 0.07
		EB-IGRT: 0.3%	
		EBRT plus HDR: 1%	
	Acute tenesmus ≥Grade 3	BT: 0%	p-value of difference: 0.18
		EB-IGRT: 0%	
		EBRT plus HDR: 0.2%	
	Acute bleeding ≥Grade 3	BT: 0%	p-value of difference:0.45
		EB-IGRT: 0.2%	
		EBRT plus HDR: 0%	
	Any acute gastrointestinal ≥Grade 3	BT: 0.2%	p-value of difference: 0.19
		EB-IGRT: 0.5%	
		EBRT plus HDR: 1%	
	Any acute genitourinary/gastrointestinal toxicity ≥Grade 3	BT: 8%	p-value of difference: 0.6
		EB-IGRT: 4%	
		EBRT plus HDR: 8%	

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Mohammed et al. 2012[39] (continued)	Late dysuria ≥Grade 3	BT: 0.6%	p-value of difference: 0.003
		EB-IGRT: 0.2%	
		EBRT plus HDR: 0.5%	
	Late frequency/urgency ≥Grade 3	BT: 2%	p-value of difference: 0.09
		EB-IGRT: 0.5%	
		EBRT plus HDR: 1%	
	Late retention ≥Grade 3	BT: 3%	p-value of difference: 0.002
		EB-IGRT: 1%	
		EBRT plus HDR: 5%	
	Late hematuria ≥Grade 3	BT: 2%	p-value of difference: 0.09
		EB-IGRT: 3%	
		EBRT plus HDR: 1%	
	Late incontinence ≥Grade 3	BT: 0.3%	p-value of difference: 0.13
		EB-IGRT: 0.4%	
		EBRT plus HDR: 1%	
	Late urethral stricture ≥Grade 3	BT: 3%	p-value of difference: <0.001
		EB-IGRT: 2%	
		EBRT plus HDR: 10%	
	Any late genitourinary ≥Grade 3	BT: 5%	p-value of difference: <0.001
		EB-IGRT: 4%	
		EBRT plus HDR: 12%	
	Late diarrhea ≥Grade 2	BT: 0.6%	p-value of difference: 0.20
		EB-IGRT: 2%	
		EBRT plus HDR: 2%	
	Late rectal bleeding ≥Grade 2	BT: 0.9%	p-value of difference: <0.001
		EB-IGRT: 16%	
		EBRT plus HDR: 7%	
	Late proctitis ≥Grade 2	BT: 0.3%	p-value of difference: <0.001
		EB-IGRT: 5%	
		EBRT plus HDR: 3%	

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Mohammed et al. 2012[39] (continued)	Late rectal incontinence ≥Grade 2	BT: 0.3%	p-value of difference: 0.005
		EB-IGRT: 3%	
		EBRT plus HDR: 0.8%	
	Late nausea ≥Grade 2	BT: 0%	p-value of difference: NA
		EB-IGRT: 0%	
		EBRT plus HDR: 0%	
	Any late gastrointestinal toxicity ≥Grade 2	BT: 2%	p-value of difference: <0.001
		EB-IGRT: 20%	
		EBRT plus HDR: 9%	
	Late diarrhea ≥Grade 3	BT: 0%	p-value of difference: 0.24
		EB-IGRT: 0%	
		EBRT plus HDR: 0.2%	
	Late rectal bleeding ≥Grade 3	BT: 0.3%	p-value of difference: 0.02
		EB-IGRT: 2%	
		EBRT plus HDR: 0.5%	
	Late proctitis ≥Grade 3	BT: 0%	p-value of difference: 0.43
		EB-IGRT: 0.5%	
		EBRT plus HDR: 0.4%	
	Late rectal incontinence ≥Grade 3	BT: 0%	p-value of difference: 0.37
		EB-IGRT: 0.4%	
		EBRT plus HDR: 0%	
	Late nausea ≥Grade 3	BT: 0%	p-value of difference: NA
		EB-IGRT: 0%	
		EBRT plus HDR: 0%	
	Any late gastrointestinal toxicity ≥Grade 3	BT: 0.3%	p-value of difference: 0.01
		EB-IGRT: 2%	
		EBRT plus HDR: 1%	
	Multivariate hazard ratio (95% CI) for decreasing PSA	NA	Cox Regression HR 1.0 (0.98–1.01), p=0.43 for any chronic genitourinary toxicity ≥2
	Multivariate hazard ratio (95% CI) for increasing age	NA	Cox Regression HR 1.03 (1.02–1.05), p<0.001 for any chronic genitourinary toxicity ≥2

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Mohammed et al. 2012[39] (continued)	Multivariate hazard ratio (95% CI) for EBRT plus HDR vs. EB-IGRT	NA	Cox Regression HR 0.98 (0.52–1.84), p=0.94 for any chronic genitourinary toxicity ≥2
	Multivariate hazard ratio (95% CI) for BT vs. EB-IGRT	NA	Cox Regression HR 1.40 (1.06–1.86), p=0.02 for any chronic genitourinary toxicity ≥2
	Multivariate hazard ratio (95% CI) for increasing % Core	NA	Cox Regression HR 1.00 (0.99–1.01), p=0.94 for any chronic gastrointestinal toxicity ≥2
	Multivariate hazard ratio (95% CI) for increasing age	NA	Cox Regression HR 1.03 (1.00–1.06), p=0.05 for any chronic gastrointestinal toxicity ≥2
	Multivariate hazard ratio (95% CI) for ADT	NA	Cox Regression HR 0.765 (0.49–1.21), p=0.25 for any chronic gastrointestinal toxicity ≥2
	Multivariate hazard ratio (95% CI) for EBRT plus HDR vs. EB-IGRT	NA	Cox Regression HR 0.19 (0.11–0.35), p<0.001 for any chronic gastrointestinal toxicity ≥2
	Multivariate hazard ratio (95% CI) for BT vs. EB-IGRT	NA	Cox Regression HR 0.16 (0.02–1.20), p=0.08 for any chronic gastrointestinal toxicity ≥2
Sheets et al. 2012[45]	Gastrointestinal procedures including colonoscopy	Intensity-modulated radiation therapy (IMRT): 6,438 patients 3D-conformal radiation therapy (3D-CRT): 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 3,011, rate 17.0 CRT total events 2,989, rate 16.6 Rate ratio: 1.02 (0.97–1.07). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 302, rate 17.7 Proton total events 347, rate 21.4 Rate ratio: 0.82 (0.70–0.97).

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Sheets et al. 2012[45] (continued)	Gastrointestinal diagnoses	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 2,594, rate 13.4 CRT total events 2,828, rate 14.7 Rate ratio: 0.91 (0.86–0.96). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 235, rate 12.2 Proton total events 301, rate 17.8 Rate ratio: 0.66 (0.55–0.79).
	Urinary nonincontinence procedures	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 483, rate 1.9 CRT total events 493, rate 1.9 Rate ratio: 0.99 (0.87 to 1.12). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 44, rate 1.8 Proton total events 42, rate 1.6 Rate ratio: 1.06 (0.69 to 1.63).
	Urinary nonincontinence diagnoses	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 1,869, rate 8.8 CRT total events 1,941, rate 8.8 Rate ratio: 0.99 (0.93 to 1.06). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 161, rate 7.5 Proton total events 144, rate 6.3 Rate ratio: 1.25 (0.99 to 1.58).

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Sheets et al. 2012[45] (continued)	Urinary incontinence procedures	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 1,888, rate 8.9 CRT total events 1,867, rate 8.5 Rate ratio: 1.05 (0.98 to 1.12). Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 161, rate 7.6 Proton total events 173, rate 7.8 Rate ratio: 0.97 (0.77 to 1.20).
	Urinary incontinence diagnoses	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 858, rate 3.5 CRT total events 917, rate 3.7 Rate ratio: 0.94 (0.86 to 1.04) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 75, rate 3.1 Proton total events 82, rate 3.3 Rate ratio: 0.96 (0.70 to 1.32)

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Sheets et al. 2012[45] (continued)	Erectile dysfunction procedures	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 200, rate 0.8 CRT total events 224, rate 0.8 Rate ratio: 0.90 (0.75–1.09) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 21, rate 0.8 Proton total events 36, rate 1.4 Rate ratio: 0.61 (0.35 to 1.06)
	Erectile dysfunction diagnoses	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to Proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 1,342, rate 5.9 CRT total events 1,239, rate 5.3 Rate ratio: 1.12 (1.03–1.20) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 145, rate 6.6 Proton total events 164, rate 7.4 Rate ratio: 0.89 (0.70 to 1.12)

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Sheets et al. 2012[45] (continued)	Hip fracture	IMRT: 6,438 patients CRT: 6,478 patients IMRT: 684 (for the propensity score matched comparison to proton radiation) Proton radiation: 684 patients	Adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. CRT: IMRT total events 209, rate 0.8 CRT total events 272, rate 1.0 Rate ratio: 0.78 (0.65 to 0.93) Propensity score matched rates adjusted for baseline- and clinical- characteristics. Outcomes are per 100 person-years and are presented as rate ratio (95% CI) for IMRT vs. Proton: IMRT total events 21, rate 0.8 Proton total events 18, rate 0.7 Rate ratio: Could not be calculated due to small number of events and zero cell counts in some of the covariates.

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Bekelman et al. 2011[40] bowel complications	IMRT: 3,727 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 18.8% (95% CI, 17.8–19.9)	3D-CRT: 4,614 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 22.5% (21.5–23.5)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.86 (0.79–0.93)
urinary complications	IMRT: 3,997 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 10.4% (95% CI, 9.6–11.1)	3D-CRT: 5,145 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 11.2% (10.4–12.0)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.93 (0.83–1.04)
erectile complications	IMRT: 4,586 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 1.0% (95% CI, 0.8–1.3)	3D-CRT: 5,946 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 0.7% (0.5–0.9)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 1.50 (1.00–2.24)
proctitis, hemorrhage complications	IMRT: 4,472 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 3.5% (95% CI, 3.0–4.0)	3D-CRT: 5,723 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 4.5% (4.0–5.0)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.78 (0.64–0.95)
cystitis, hematuria complications	IMRT: 4,226 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 7.7% (95% CI, 7.0–8.4)	CRT: 5,433 patients at risk 24 month cumulative incidence of complication requiring an invasive procedure 8.3% (7.6–9.0)	Multivariate HR (95% CI) adjusted for propensity score, year of diagnosis, and area population. HR 0.94 (0.83–1.07)

Table 67. Reported adverse events (nonrandomized comparative studies) (continued)

Study	Adverse Events/Harms Reported		Author Reported Calculations
Williams et al. 2011[37]	Brachytherapy: 9,985 patients	Cryotherapy: 943 patients	Propensity-weighted incidence of complications expressed as percentages.
Overall complications	63.6%	48.8%	P<0.001
Urinary cystitis	0.5%	2.4%	P<0.001
Urinary retention	24.5%	8.4%	P<0.001
Urethral stricture	5.4%	3.7%	P=0.190
incontinence	18.2%	11.3%	P<0.001
Urethral fistula	0.9%	0.3%	P=0.1445
Bowel	12.1%	19.0%	P<0.001
Proctitis/hemorrhage	11.7%	18.6%	P<0.001
Rectal injury/ulcer	0.8%	2.0%	P<0.001
ED	34.7%	21.0%	P<0.001

Appendix H. Ongoing Clinical Trials

Table 68. Ongoing clinical trials within the United States (http://clinicaltrials.gov/ct2/home)

Identifier	Sponsor	Design	Purpose	Start Date and Expected Completion Date
NCT00430183	Cancer and Leukemia Group B, USA	Randomized Controlled Trial (RCT)	This randomized phase III trial is studying docetaxel and leuprolide or goserelin to see how well they work when given before surgery compared with surgery alone in treating patients with high-risk localized prostate cancer	Start Date: December 2006 Estimated Completion Date: June 2018 Estimated Enrollment: 750
NCT01617161	Massachusetts General Hospital, University of Pennsylvania, National Cancer Institute	RCT	This randomized phase III trial is studying whether men being treated for prostate cancer have the same amount of side effects from either one of two different external radiation treatments: intensity-modulated radiation therapy or proton beam therapy	Start Date: July, 2012 Estimated Completion Date: June 2016 Estimated Enrollment: 750
NCT01365143	Mayo Clinic, USA	RCT	This study will prospectively randomize patients with localized prostate cancer who are candidates for surgical management to open versus robotic radical prostatectomy.	Start Date: May 2011 Estimated Completion Date: May 2016 Estimated Enrollment: 454
NCT01492972	Proton Collaborative Group, USA	RCT	This study will compare the use of hypofraction proton therapy (28 treatments) alone to proton therapy with androgen suppression therapy	Start Date: January 2012 Estimated Completion Date: December 2021 Estimated Enrollment: 192
NCT00175383	University of British Columbia, Canada	RCT	This study will compare short versus long acting LHRH agonist preparation prior to transperineal implantation of the prostate.	Start Date: December 2004 Estimated Completion Date: June 2013 Estimated Enrollment: 100

Table 69. Ongoing clinical trials outside the United States (http://www.epi.bris.ac.uk/protect/)

Identifier	Sponsor	Design	Purpose	Start Date and Expected Completion Date
ProtecT (Prostate testing for cancer and Treatment) Study	Department of Health, UK	Randomized Controlled Trial	The study aims to evaluate treatments for localized prostate cancer. It is comparing surgery (radical prostatectomy), radiotherapy (radical conformal) and active monitoring (monitoring with regular check-ups).	Start date: June 1999 Estimated Completion Date: June 2013 Between June 2001 and October 2008, approximately 109,750 men have taken part in the ProtecT study.